



Guidance on dossier evaluation for the registration of pest control products in Kenya

Mechteld ter Horst, June Akinyi Aluoch, Maurice Wanyonyi Barasa, Saskia Bosman-Hoefakker, Jessica Broeders, Jacobijn van Etten, Esther de Jong, Paul N. Ngaruiya, Anne Steenbergh, Harold van der Valk, Githaiga Wagate, Sarah Muthoni Wambugu, Maureen Nekoye Waswa, Louise Wipfler

Guidance on dossier evaluation for the registration of pest control products in Kenya

Mechteld ter Horst¹, June Akinyi Aluoch⁴, Maurice Wanyonyi Barasa⁴, Saskia Bosman-Hoefakker², Jessica Broeders², Jacobijn van Etten², Esther de Jong², Paul N. Ngaruiya⁴, Anne Steenbergh², Harold van der Valk³, Githaiga Wagata⁴, Sarah Muthoni Wambugu⁴, Maureen Nekoye Waswa⁴, Louise Wipfler¹

1 Wageningen Environmental Research

2 Dutch Board for the Authorisation of Plant Protection Products (Ctgb)

3 Falconsult

4 Kenyan Pest Control Products Board (PCPB)

This research was (partly) funded by the Dutch Ministry of Agriculture, Nature and Food Quality

Wageningen Environmental Research
Wageningen, December 2019

Approved for publication:
M. de Potter

Report 2979
ISSN 1566-7197

Ter Horst, M.M.S., Aluoch, J.A., Barasa, M.W., Bosman-Hoefakker, S., Broeders, J., Van Etten, J., De Jong, E., Ngaruiya, P.N., Steenberg, A., Van der Valk, H., Wagate, G., Wambugu S.M., Waswa, M.N., Wipfler, E.L. 2019. *Guidance on dossier evaluation for the registration of pest control products in Kenya*. Wageningen, Wageningen Environmental Research, Report 2979. 94 pp.; 20 fig.; 11 tab.; 46 ref.

This document describes guidance on dossier evaluation for the registration of pest control products in Kenya. The document provides guidance for the assessment of a limited number of aspects that are part of evaluation of a pest control product registration dossier. It should therefore not be considered as a complete pesticide evaluation manual, though it is intended to contribute to a future complete pest control product evaluation manual for Kenya. The guidance should be read together with an implementation report which contains stepping stones for further development.

The guidance was developed within the *Pesticide management initiative East African Region: Kenya* (PEAR-Kenya) project. The project ran in the period 2016 – 2019 and was sponsored and supported by the Dutch Ministry of Agriculture, Nature and Food Quality and the Embassy of the Netherlands in Nairobi.

The guidance addresses various aspects of a pest control product evaluation covering low risk pest control products, microbial pest control product, chemical pest control products and equivalence determination. The evaluation procedures developed covers a fast-track pathway for low risk products. For microbial products the procedure focusses on identification, human pathology and infectiveness and hazard and risk assessments for metabolites of potential concern. For chemical products the procedure includes methods for human health and pollinator risk assessments. The evaluation process of new pest control products can be speeded up if the active ingredient or active agent of a new product proves to be equivalent to an already registered product.

Keywords: Kenya, pest control, registration, Pest Control Products Board, risk assessment, human health, environment, pesticides, microbial pest control agent, metabolite, consumer, operator, pollinator.

The pdf file is free of charge and can be downloaded at <https://doi.org/10.18174/510074> or via the website www.wur.nl/environmental-research (scroll down to Publications – Wageningen Environmental Research reports). Wageningen Environmental Research does not deliver printed versions of the Wageningen Environmental Research reports.

 2019 Wageningen Environmental Research (an institute under the auspices of the Stichting Wageningen Research), P.O. Box 47, 6700 AA Wageningen, The Netherlands, T +31 (0)317 48 07 00, www.wur.nl/environmental-research. Wageningen Environmental Research is part of Wageningen University & Research.

- Acquisition, duplication and transmission of this publication is permitted with clear acknowledgement of the source.
- Acquisition, duplication and transmission is not permitted for commercial purposes and/or monetary gain.
- Acquisition, duplication and transmission is not permitted of any parts of this publication for which the copyrights clearly rest with other parties and/or are reserved.

Wageningen Environmental Research assumes no liability for any losses resulting from the use of the research results or recommendations in this report.



In 2003 Wageningen Environmental Research implemented the ISO 9001 certified quality management system. Since 2006 Wageningen Environmental Research has been working with the ISO 14001 certified environmental care system.

By implementing the ISO 26000 guideline, Wageningen Environmental Research can manage and deliver its social responsibility.

Contents

	Verification	5
	Preface	7
1	General introduction	9
	1.1 Objectives of the guidance document	9
	1.2 Legal basis for the evaluation of pest control products in Kenya	10
	1.3 Quality of data	10
	1.3.1 Test guidelines	10
	1.3.2 Good laboratory practice	11
	1.3.3 How to check studies for OECD and GLP compliance	11
2	Overall framework for the evaluation of pest control products in Kenya	13
3	Fast track procedure for low risk pest control products	16
	3.1 Justification	16
	3.2 Evaluation procedure	16
	3.3 Applicability of the fast track procedure	18
4	Evaluation of microbial pest control agents (MPCAs)	19
	4.1 Introduction	19
	4.2 Proposed framework for the evaluation of MPCAs in Kenya	19
5	Evaluation of chemical pest control agents – human health risk assessment	26
	5.1 Introduction	26
	5.2 Framework for human health risk assessment	28
	5.3 Hazard assessment – Adoption of toxicological reference values	29
	5.3.1 The Acceptable Daily Intake (ADI)	29
	5.3.2 The Acute Reference Dose (ARfD)	30
	5.3.3 The Acceptable Operator Exposure Level (AOEL)	31
	5.4 Occupational risk assessment	32
	5.4.1 Operator risk assessment	33
	5.4.2 Worker risk assessment	37
	5.4.3 Resident risk assessment	39
	5.5 Consumer risk assessment	40
	5.5.1 Introduction	40
	5.5.2 Chronic dietary risk assessment	41
	5.5.3 Acute dietary risk assessment	41
	5.6 Bridging human health risk assessments	42
6	Evaluation of chemical pest control agents – environmental risk assessment	44
	6.1 Introduction	44
	6.2 Framework for pollinator risk assessment	44
	6.2.1 Principles of the pollinator risk assessment	44
	6.2.2 Risk assessment scheme	45
	6.2.3 Step 1 – Probability and routes of exposure	45
	6.2.4 Step 2 – Tier-I risk assessment	47
	6.2.5 Step 3 – Refinement of Tier-I risk assessment	49
	6.2.6 Step 4 – Tier-II risk assessment	49
	6.2.7 Decision making	50

7	Registration by equivalence	51
7.1	Introduction	51
7.2	Equivalence evaluation of chemical pesticides	51
7.3	Equivalence evaluation of microbial pest control agents	52
	References	53
Annex 1	EU low risk criteria and US-EPA minimum risk criteria	56
Annex 2	Guidance on using the EU 'low risk active substance' list and the US-EPA 'minimum risk pesticides' list	58
Annex 3	Guidance on the equivalence evaluation for microbial agents for Kenya	60
Annex 4	Guidance on registration by analogy	66
Annex 5	Registration by analogy check-list and guidance for microbial pest control products	68
Annex 6	No Observed Adverse Effect Level (NOAEL)	71
Annex 7	Instruction for downloading the EFSA AOEM model	73
Annex 8	Step by Step guidance for performing risk assessment for operators in the field	74
Annex 9	Step by Step guidance for performing risk assessment for workers in the field	79
Annex 10	Step by Step guidance for performing risk assessment for residents	81
Annex 11	Step by Step guidance for performing chronic risk assessment for consumers	83
Annex 12	Step by Step guidance for performing acute risk assessment for consumers	86
Annex 13	Background information relevant for the consumer/ dietary risk assessment	89

Verification

Report: 2979

Project number: 5200042849

Wageningen Environmental Research (WENR) values the quality of our end products greatly. A review of the reports on scientific quality by a reviewer is a standard part of our quality policy.

This report is a product of and has been approved by the Kenyan-Dutch project group on strengthening the registration of pest control products in Kenya.

Approved team leader responsible for the contents,

name: M. de Potter

date: 17 December 2019

Preface

This document describes guidance on dossier evaluation for the registration of pest control products in Kenya. It goes together with an implementation report which contains stepping stones for further development, and as such both contribute to a future complete pesticide evaluation manual for Kenya.

The report is the result of intensive collaboration between the PCPB and Dutch partners in the *Pesticide management initiative East African Region: Kenya* (PEAR-Kenya), work package B. The PEAR-Kenya project aims to contribute to sustainable agricultural production in Kenya through improving plant health, risk assessment, Integrated Pest Management (IPM), food safety and reducing the risks of pesticide use. The PEAR-Kenya project's specific aims are to stimulate Integrated Pest Management (IPM) and to improve the structure, clarity and the procedures of pest control product registration such that key products for Integrated Pest Management will be registered and become available on the market, without lowering (environmental) quality standards.

In work package B of the project joint efforts have been made to strengthen the administrative process and to review and further develop risk assessment procedures, both for low risk and for non-low risk pest control products. The work resulted in the guidance for evaluation of pest control products described in the present document.

The project has been executed in collaboration with the Kenyan Pest Control Product Board (PCPB) and other stakeholders active in the field of plant protection and IPM, e.g. Ministry of Agriculture, Livestock and Fisheries, biological producers, chemical producers, farmers organisations, the International Centre of Insect Physiology and Ecology (ICIPE) and Jomo Kenyatta University of Agriculture and Technology (JKUAT). Also the Dutch authorities: the Dutch Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) and The Netherlands food and consumer product safety authority (NVWA) were part of the project.

We thank the Dutch Ministry of Agriculture, Nature and Food Quality as well as the Embassy of the Netherlands in Nairobi for sponsoring and supporting this activity as part of the PEAR-Kenya project.

Louise Wipfler
Project manager PEAR-Kenya project

1 General introduction

1.1 Objectives of the guidance document

The present document is a draft guidance document describing improved procedures on dossier evaluation for the approval of pest control products in Kenya. At the same time, it will enhance the transparency of the registration process and provides potential applicants with dedicated information on how dossiers are evaluated. The guidance for evaluation is limited to pest control products that are used as plant protection products.

Over the last decades OECD and FAO have developed many guidance documents that are dedicated to specific aspects of pesticide evaluation. When feasible these guidance documents are referred to.

This document is accompanied by an implementation guide (Ter Horst et al., 2019), which provides background information and suggestions for steps that can be taken to further develop and implement the evaluation procedure for pest control products in Kenya. The implementation guide can be used in follow up discussions with Kenyan stakeholders. It provides reflections on some of the methods proposed and also information and/or advice on what is needed (e.g. verifying underlying data of models, decision making) to implement the guidance proposed in this guidance document.

The evaluation of pest control products concerns several aspects.

- The composition and physical-chemical properties of active ingredients and pest control products should be evaluated to prevent products being placed on the market which: 1. are of insufficient quality, resulting in reduced applicability or reduced efficacy 2. may cause risks to the user, public health and the environment. Physical-chemical properties of a formulation are also important from a safety point of view. Aspects such as flammability of the product and the presence of undesirable impurities can be relevant for a safe use.
- The effectiveness of each pest control product for its intended purpose should be established. If adequate efficacy against the target organism(s) cannot be shown, no justification for registration exists.
- It should be established whether the application of a product has no adverse consequences for operators, workers, bystanders and residents. It should also be established if the use of pest control products results in residues in foodstuffs and drinking water hence posing risks for human health.
- It should be established that the application of a product has no adverse effects on the environment.
- Labelling, packaging, hazard classification, disposal, precautions for use and treatment in case of poisoning should all meet national or international criteria and/or be feasible under Kenyan conditions of distribution and use.

This document provides guidance for the assessment of only a limited number of aspects that are part of evaluation of a pesticide registration dossier. These aspects are:

- Low risk pest control products
- Microbial pest control products
- Chemical pest control products – human health risk assessment
- Chemical pest control products – pollinator risk assessment
- Equivalence determination

Other aspects of a pest control product evaluation, as outlined above, are not included in the guidance. The guidance document should therefore not be considered as a complete pesticide evaluation manual, though it may contribute to such a manual at a later stage.

1.2 Legal basis for the evaluation of pest control products in Kenya

The legal basis for pesticide registration in Kenya is the Pest Control Products Act ¹.

A pest control product is defined in this Act as: a product, device, organism, substance or thing that is manufactured, represented, sold or used as a means for directly or indirectly controlling, preventing, destroying, attracting or repelling any pest and includes —

- a.** *any compound or substance that enhances or modifies or is intended to enhance or modify the physical or chemical characteristics of a pest control product to which it is added; and*
- b.** *any active ingredient used for the manufacture of a pest control product.*

A pest is defined as: any injurious, noxious or troublesome insect, fungus, bacterial organism, virus, weed, rodent or other plant or animal pest; and includes any injurious, noxious or troublesome organic function of a plant or animal.

Section 4.1 then stipulates that: *No person shall import into, or sell in, Kenya any pest control product unless that product has been registered, packaged and labelled in accordance with regulations made under this Act and conforms to the standards specified in those regulations.*

Therefore, on the basis of the provisions and definitions of the Act, registration is required for all types of pesticide products or active ingredients (e.g. chemical, biological, mechanical) for all uses (e.g. agricultural, domestic, public health, industrial), and including adjuvants and other functional co-formulants.

The Pest Control Products Act also establishes the Pest Control Products Board, which is the statutory body responsible to implement the provisions of the Act. Under the Act, a number of Regulations has been adopted, of which several are of direct importance to pesticide registration:

- Pest Control Products (Registration) Regulation ²;
- Pest Control Products (Labelling, Advertising and Packaging) Regulations ³ ;
- Pest Control Products (Licence Fees and other Charges) Regulations ⁴.

1.3 Quality of data

The data provided by the applicant should be of high quality and reliability: the studies should be conducted according to internationally accepted test guidelines, and with an acceptable code of Good Laboratory Practice (GLP).

1.3.1 Test guidelines

Whenever possible, all toxicity studies, studies on environmental fate and behaviour and studies needed to establish physical chemical properties must be conducted in accordance with the OECD Guidelines for the Testing of Chemicals or other internationally recognised test guidelines e.g. US Environment Protection Agency (EPA), and comply with the principles of Good Laboratory Practice (GLP).

Efficacy and residue data should be gathered according the guidelines of the East African Community.

¹ Pest Control Products Act. Chapter 346. Revised edition 2012 [1985].

² Pest Control Products (Registration) Regulations. Chapter 346, Subsidiary. Revised edition 2012 [1984].

³ Pest Control Products (Labelling, Advertising and Packaging) Regulations. Chapter 346, Subsidiary. Revised edition 2012 [1984].

⁴ Pest Control Products (Licence Fees and other Charges) Regulations. Chapter 346, Subsidiary. Revised edition 2012 [2006].

OECD test guidelines:

<http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/oecdguidelinesforthetestingofchemicals.htm> (website last entered: 4 November 2019)

Prequalification Team (formerly WHO Pesticide Evaluation Scheme (WHOPES)). Guidelines for testing. <https://www.who.int/whopes/resources/en/> (website last entered: 11 October 2019)

US EPA test guidelines:

<https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/master-list-test-guidelines-pesticides-and-toxic> (website last entered: 11 October 2019)

Efficacy and residue trials should be conducted, reported and evaluated according the guidelines of the East African Community (EAC, 2019a and EAC, 2019b).

1.3.2 Good laboratory practice

Data should be generated in accordance with sound scientific and experimental procedures and experiments performed after 25 July 1993 must have been performed in accordance with the guidelines of Good Laboratory Practice (GLP), since by then all OECD countries had adapted these guidelines.

GLP is a quality system concerned with the organisational processes and conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. The GLP regulation has no influence on the scientific aspects of study conduct, but does impact study quality, through aspects such as record keeping, thus ensuring that any study can be easily 'reconstructed' from the raw data records of the study.

Generally, open literature does not meet internationally recognized testing guidelines or GLP regulation and is therefore usually considered as supplementary information.

WHO has published a handbook on GLP: <http://www.who.int/tdr/publications/documents/glp-handbook.pdf> (website last entered on October 11, 2019).

1.3.3 How to check studies for OECD and GLP compliance

In the application forms⁵, the applicant has to indicate and provide evidence whether the study was performed according to international test guidelines (and which ones), and whether the study was conducted under GLP.

Quick scan

In the study report, the test guideline is most easily checked by looking for a statement signed by the study director, indicating in accordance to which test guideline the study was performed. The report should also indicate if there were deviations or amendments to these guidelines. Sometimes, the test protocol or guidelines are mentioned on the first page.

The GLP status can be checked by looking for a Quality Assurance statement in the study report, which must include the dates of several internal QA inspections of the study. The GLP statement must be signed by the QA officer. Ideally, an official GLP certificate is included in the report.

The study should be performed by a laboratory with an OECD-GLP accreditation. If the accreditation status is unknown the laboratory in the dossier will be contacted and asked to provide documents. Also the laboratory will be asked to confirm that the provided study is known to them.

⁵ Applications forms can be downloaded from the PCPB website: <http://www.pcpb.go.ke/application-forms/> ; last entered October 11, 2019.

Detailed evaluation

The identity of the tested substance and the tested product, and the purity of the tested substance should be clearly stated for each study. In the context of the influence that impurities can have on toxicological behaviour, it is essential that for each study submitted, a detailed description (specification) of the material used is provided. Tests should be conducted using active ingredient of that specification to be used in the manufacture of preparations to be authorised, except where radiolabelled material is required or permitted.

The OECD test guidelines for various types of study can be found on:

<http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/oecdguidelinesforthetestingofchemicals.htm> (last entered on 11 October 2019).

These guidelines are internationally accepted and recommended. Section 1 of these guidelines contains guidelines for studies of physico-chemical properties and section 2 contains the guidelines for studies of environmental (biotic) effects. Section 3 contains guidelines on environmental fate and behaviour and section 4 of these guidelines contains the guidelines for studies on health effects. Click on the English version under health effects. Thereafter, by clicking on 'Title', the test guidelines will appear according to ascending guideline number.

2 Overall framework for the evaluation of pest control products in Kenya

To assess whether a pest control product (and its active ingredient(s)/agent(s)) can be approved for registration, PCPB evaluates various technical and scientific aspects of the product and its use. These include, but are not limited to:

- Biological efficacy
- Physical and chemical characteristics
- Residues
- Human health hazards and risks
- Environmental hazards and risks
- Labelling, packaging, disposal

These evaluations fit within an overall framework for evaluation, which is primarily based on the type of pest control product being submitted to PCPB for registration.

The framework is based on the following principles:

- Administrative procedures as defined in legislation are followed;
- Internationally recognized procedures are adhered to, whenever present and applicable to Kenya;
- A tiered approach, to optimize the use of resources both at PCPB and for the applicant, is applied if possible:
 - start with less complex assessments, allowing fast-track registration, whenever feasible;
 - require more detailed data and evaluations, only if needed.

The main elements of this framework are shown in Figure 1.

1. Efficacy

For a pest control product to be authorized for use in Kenya, it has to be efficacious against the target pests for which registration is sought. In principle, efficacy has to be shown by the applicant against all pests/diseases/weeds in all crops that are to be listed on the label.

If a pest control product is not efficacious for a given pest-crop combination, no justification exists to register the product for that pest-crop combination. However, the applicant may modify the Good Agricultural Practice (GAP) to achieve efficacy (e.g. change the application rate, frequency, timing, etc.).

These uses that result in efficacious pest control are subsequently specified in a table of intended uses, or Good Agricultural Practice (GAP) table. The GAP table is the basis for the *directions for use* on the label and also for the human health and environmental risk assessments.

In this document, no guidance is provided on the evaluation of efficacy trial data submitted by the applicant. PCPB has published an efficacy evaluation protocol for pest control products in Kenya, with the aim to harmonize efficacy testing and reporting⁶. Furthermore, harmonized regional *Procedures for evaluating & reporting the efficacy of pest control agents for plants* have been adopted by the East African Community (EAC).

2. Equivalence

If the active ingredient (a.i.) of a chemical pesticide, or the microbial pest control agent (MCPA) of a biological pesticide, have previously been registered in Kenya, registration of a new pest control product containing the same a.i. or MCPA may sometimes be fast-tracked. This is possible if the active ingredient or MCPA in the new products is equivalent to the already registered one.

⁶ <http://www.pcpb.go.ke/protocol-on-efficacy-trials/> (website last entered: 11 October 2019)

Equivalence means the determination of the similarity of the impurity and toxicological profile, as well as of the physical and chemical properties, presented by supposedly similar technical material originating from different manufacturers, in order to assess whether they present similar levels of risk (FAO/WHO, 2016).

If the a.i. or MCPA of the new product is equivalent to the already registered one, the toxicological and environmental evaluation of the new product can be partly waived, speeding up the evaluation process.

The equivalence evaluation procedures are outlined in Chapter 7.

3. Low risk products

Next, the framework includes a fast-track pathway for low risk pest control products.

Products containing active ingredients or MCPAs that have been classified as (potentially) low risk by reputable regulators (presently the European Union, EU, or the US Environmental Protection Agency, US-EPA) do not require a full human health or environmental risk assessment.

In view of promoting the use of low risk products in agriculture in Kenya, a fast track procedure for these products may make these (relatively new) types of products more easily available to farmers.

The procedure for identification of low risk pest control products is outlined in Chapter 3.

4. Microbial pest control products

Microbial pest control products have very different properties from chemical pesticides and will therefore show different efficacy and pose different human health and environmental risks. Evaluating microbial pest control products on the basis of the procedures and criteria used for chemical pesticides may therefore lead to erroneous registration decisions.

Microbial pest control products are therefore evaluated following a dedicated procedure, which is outlined in Chapter 4.

5. Chemical pest control products

PCPB uses various methods to evaluate the hazards and risks of chemical pest control products. In this guidance document, some of these methods have been further enhanced.

The present version of the guidance document describes the following evaluation procedures for chemical pest control products:

- Human health risk assessment (Chapter 5)
 - Hazards assessment
 - Occupational risk assessment
 - Residents risk assessment
 - Dietary risk assessment
- Environmental risk assessment (Chapter 6)
 - Pollinator risk assessment

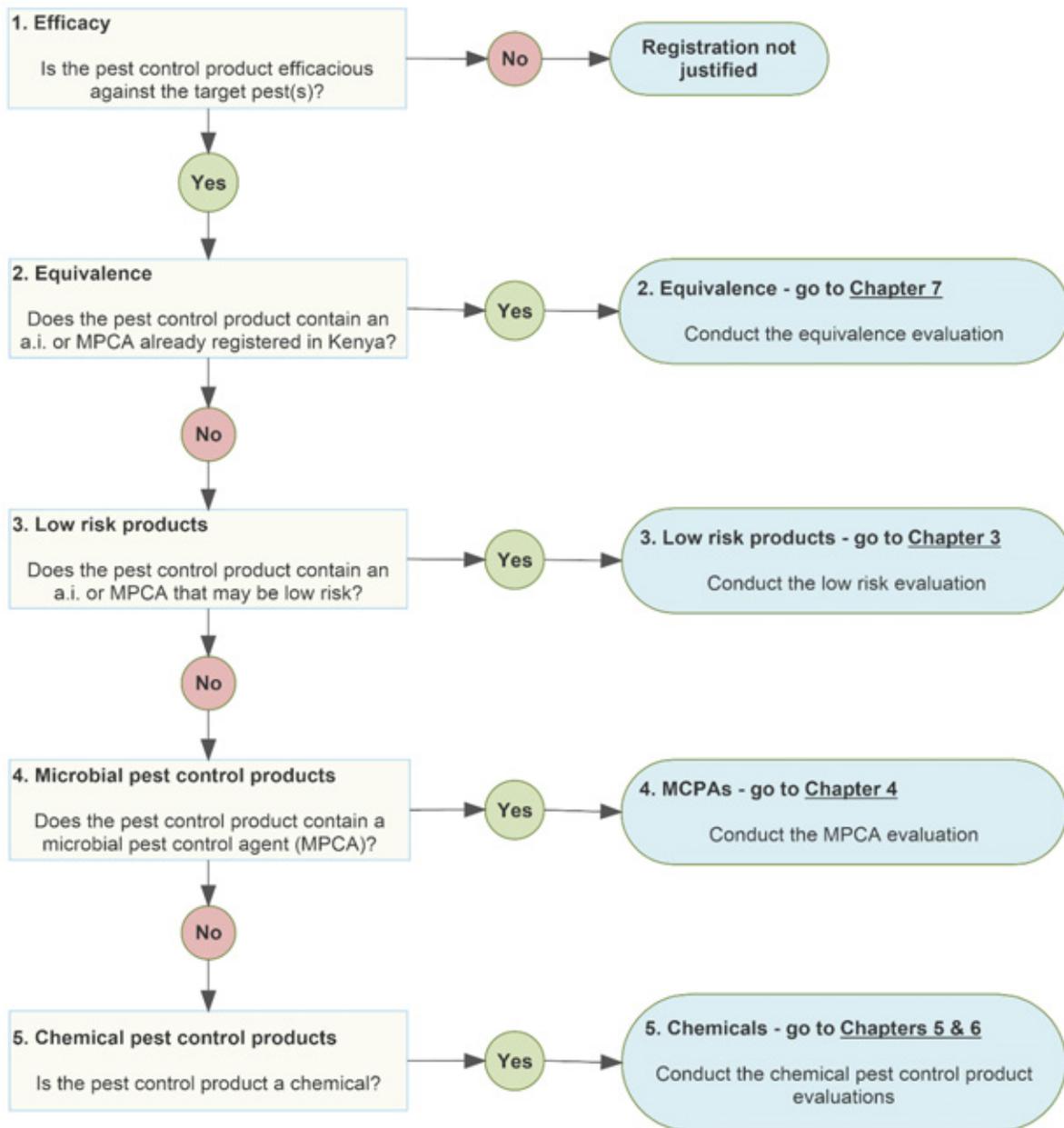


Figure 1 General framework for the evaluation of pest control products in Kenya.

3 Fast track procedure for low risk pest control products

3.1 Justification

The use of low risk pesticides (especially low-risk biopesticides) is a key component for pest control in an Integrated Pest Management approach. To stimulate IPM a fast track procedure for identifying and evaluating low risk pest control products was developed with the objective to speed up the authorisation process for these products.

The procedure makes optimal use of the identification of low risk pesticides by reputable pesticide registration authorities, such as the European Union (EU) and the US Environmental Protection Agency (US-EPA).

In the EU low risk identification is based on the criteria outlined in Annex 1. Annex 1 also provides the criteria upon which the so-called minimum risk identification in the US is based.

Furthermore, procedures for evaluation by analogy developed by FAO are used as a basis for the fast track procedure.

3.2 Evaluation procedure

The fast track evaluation procedure for low risk pest control products is applicable both to low risk chemical pesticides (including semiochemicals and botanicals) and microbial pest control agents (MPCAs). The procedure follows the following steps (see also Figure 2):

1. Identification of low risk active ingredient or MPCA
2. Assessment of similarity with the reference low risk active ingredient or MPCA
3. Evaluation of analogy with the low risk reference pest control product

For each of the steps guidance is provided in following sections.

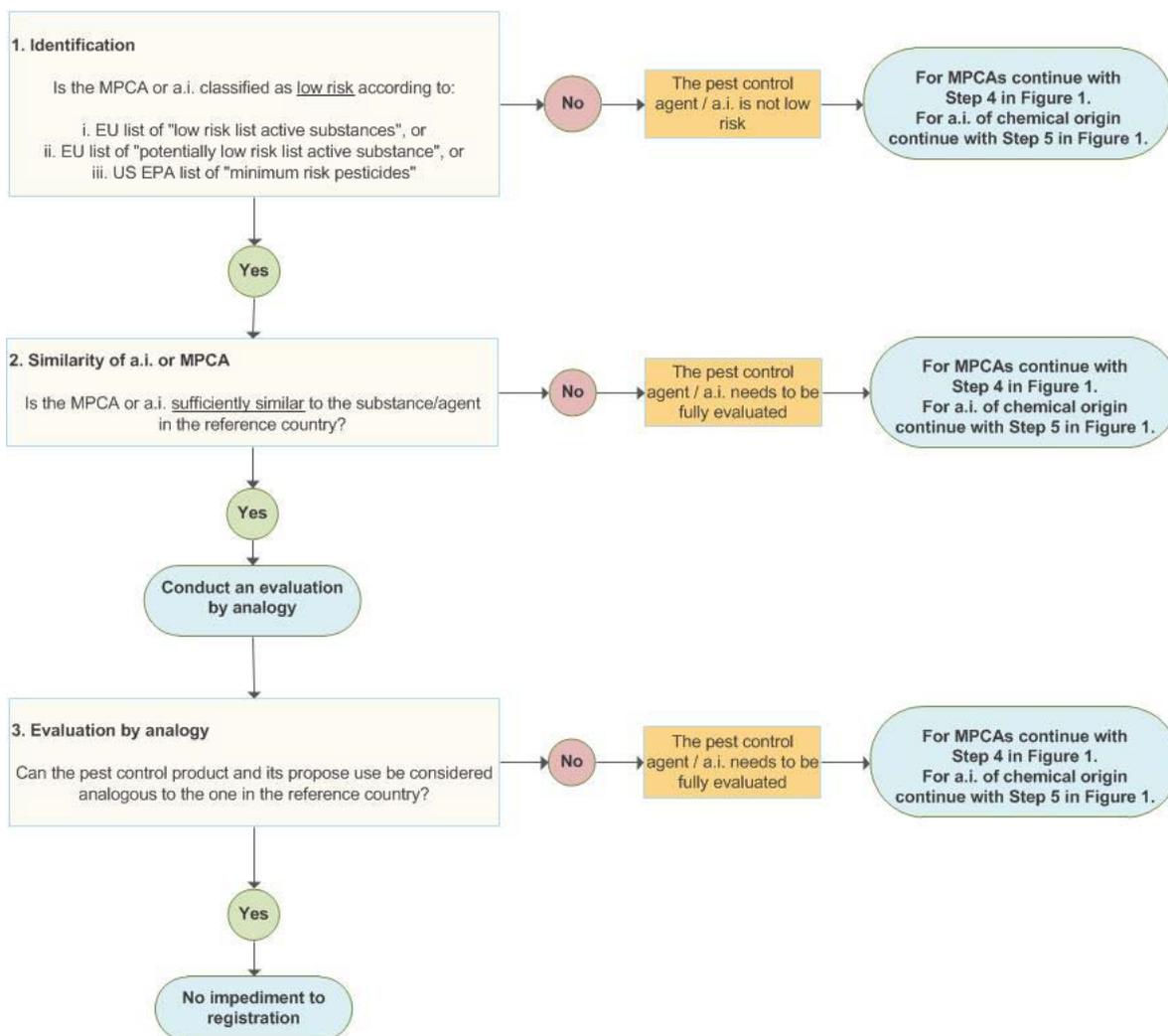


Figure 2 Flow chart for the evaluation of low risk pest control products.

1. Identification of low risk active ingredients/agents

Active ingredients or microbial pest control agents are considered to be low risk, if they are classified as:

1. Authorized low risk active substance by the EU; or
2. Potential low risk active substance by the EU; or
3. Minimum risk pesticide by the US-EPA.

This information can be obtained from the web sites of the EU and the US-EPA. Detailed guidance is given in Annex 2.

2. Assessment of similarity

If the active substance/agent of the local product for which registration is requested is classified as low-risk or potentially low-risk by the EU, or as minimum risk pesticides by the US-EPA, it is checked whether the active substance/agent of the local product is 'sufficiently similar' to the active substance/agent classified as low-risk or potentially low-risk by the EU or as minimum risk pesticide by the US-EPA.

The terminology 'sufficient similar' is used instead of 'equivalence'. The reason is that a full equivalence assessment with the EU or US-EPA is not possible because the reference specification is considered to be confidential information and is therefore in case of the EU, only accessible for registration authorities from EU member states, but not by PCPB.

No specific guidance is developed to assess whether the active substance/agent of the local product is sufficiently similar to the active substance/agent classified as low-risk or potentially low-risk by the EU or as minimum risk pesticides by the US-EPA.

For products containing active substances of chemical origin (incl. botanicals and semiochemicals), the assessment is made based on:

- The minimum purity of the active substance,
- The maximum content of the relevant impurity/impurities and
- The manufacturing process (not producing other relevant impurities).

Further guidance on how to evaluate these parameters are provided in FAO/WHO (2016).

Furthermore, the FAO guidance for registration by analogy provides some criteria that can be used to decide that a pest control product is sufficiently similar to a reference product.

For microbial agents the assessment is made based on:

- i. The strain is identical
- ii. The content of relevant metabolites complies with the maximum limit set⁷
- iii. The content of microbial contaminants complies with the OECD issue paper (ENV/JM/MONO(2011)43; see list of references for link to website).

Further guidance on how to evaluate these parameters is provided in Annex 2.

3. Evaluation by analogy

For active substances/agents found to be sufficiently similar to an active ingredient/agent classified as low-risk or potentially low-risk by the EU or as minimum risk pesticides by the US-EPA the **third** step is the comparison of risk/hazards of the **formulated product** using evaluation by analogy following the FAO method 'Registration by Analogy'⁸.

Evaluation by analogy uses a limited comparison between a pest control product submitted for authorization, and a similar product in one or more reference countries. Evaluation by analogy is based on the assumption that pesticide quality, efficacy and risks are considered/found acceptable in the reference country, where the product is registered. The registration authority subsequently evaluates whether the efficacy and risk of the same pesticide are also likely to be acceptable in its own country. More detailed guidance is given in Annex 4 and Annex 5.

Evaluation by analogy is possible if a pest control product has already been registered for identical or similar uses in a country considered as a reference for Kenya. For low risk products the EU and the USA are proposed as reference.

The registration status of active ingredients or formulated products in the EU and the USA (but also other countries or regions) can be found through the module 'Information Sources – Registrations Elsewhere' in the FAO Pesticides Registration Toolkit (FAO, 2019).⁹

3.3 Applicability of the fast track procedure

In case of the following situations the fast track procedure is not applicable:

- The local product cannot be classified as low risk;
- The local active ingredient/agent is not sufficiently similar to the active ingredient/agent authorized in one or more reference countries;
- The conclusion of the 'Registration by Analogy' method may be that risks are likely to be higher than in a country with a reputable registration system.

⁷ Exact values of metabolite level in batches are generally not publicly available. Therefore the maximum limit is used instead.

⁸ Most of the text below describing registration by analogy is taken directly from the website on the FAO toolkit for registration of pesticides (FAO, 2019). <http://www.fao.org/pesticide-registration-toolkit/registration-tools/registration-strategies/registration-by-analogy/en/> (website last entered: 11 October 2019).

⁹ <http://www.fao.org/pesticide-registration-toolkit/information-sources/registrations-elsewhere/en/> (website last entered: 11 October 2019).

4 Evaluation of microbial pest control agents (MPCAs)

4.1 Introduction

The EU defines a microorganism as any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material.

Due to the ability of microorganisms to proliferate, there is a clear difference between chemical active substances and microbial active substances. Hazards arising from microbial active substances are not necessarily of the same nature as chemicals and these differences should be taken into account in the assessment. Therefore, a separate framework was developed for the evaluation of MPCAs for which the fast track procedure cannot be applied.

Like in the EU, approval of microbial active agents is done on strain/isolate level (Figure 3). An exception is the group of Baculoviruses which should be approved on species level.

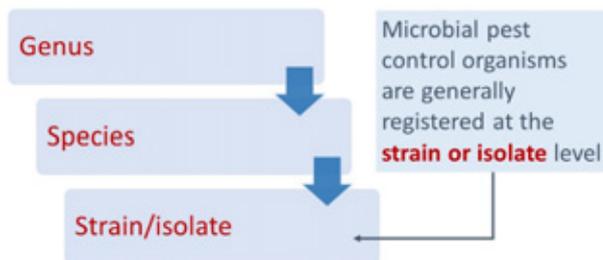


Figure 3 Taxonomic levels of microbial pest control organisms.

4.2 Proposed framework for the evaluation of MPCAs in Kenya

The framework for the evaluation of MPCAs for those MPCAs for which the fast track procedure cannot be applied or for MPCAs which do not pass the fact track procedure is given in Figure 4. The different elements in the proposed framework for the evaluation of MPCAs in Kenya are explained in the following sections¹⁰.

¹⁰ Part of the texts in the following sections are taken from the evaluation manual for biopesticides from the Dutch Board for the Authorisation of plant protection products and biocides, Ctgb, (Ctgb, 2018).

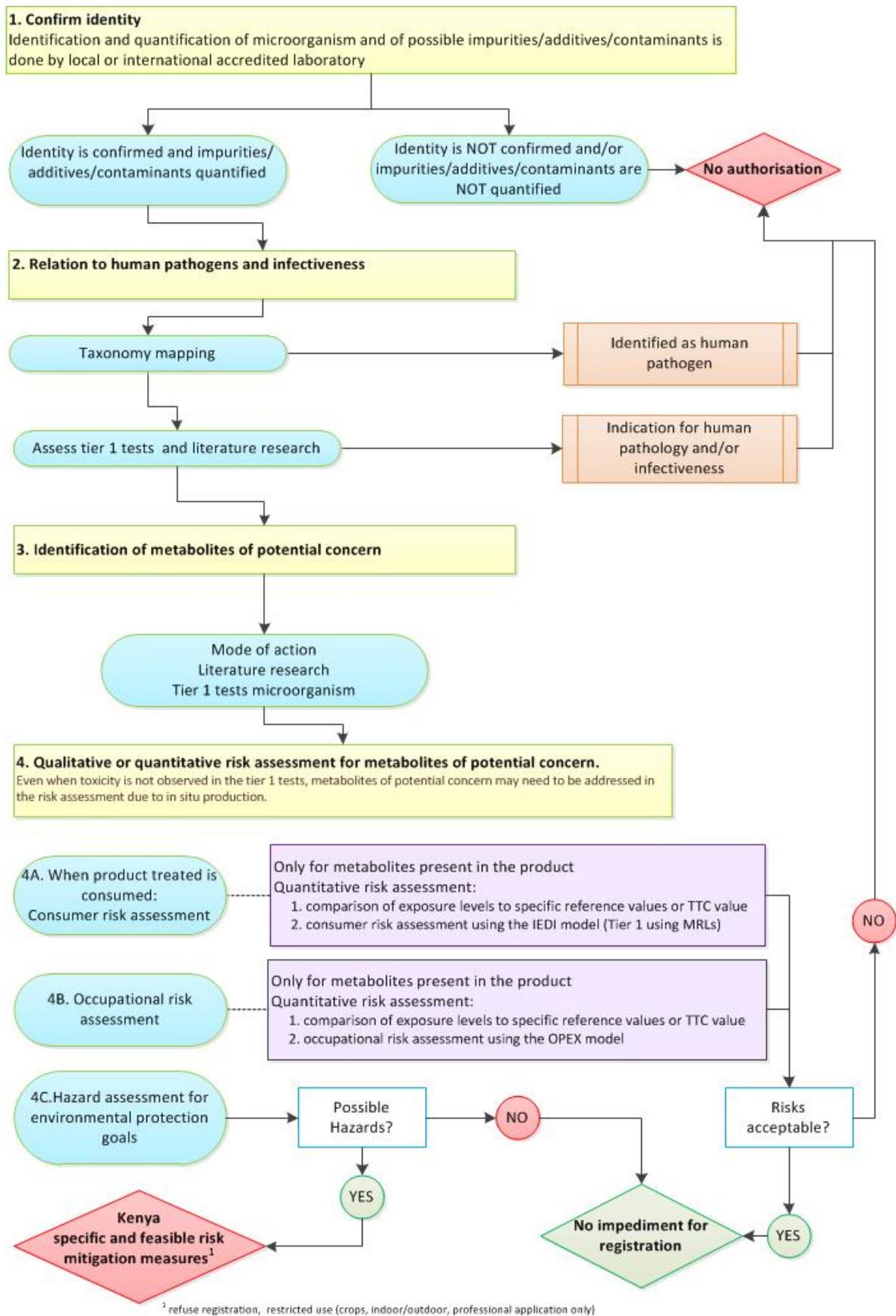


Figure 4 Flow chart for Microbial Pest Control Agents (MPCAs).

1. Identity

The microbial pest control agent should be identified and named at the strain level, except for Baculoviruses that can be identified at species level (step 1 in Figure 4).

Identification and quantification of microorganism and of possible impurities/additives/contaminants should be provided in the dossier. The applicant should also submit the method to determine the identity of the MPCA as part of the active substance dossier.

PCPB may cross-check the identification and quantification of a microbial agent and possible impurities, additives and/or contaminating microorganisms and metabolites¹¹ by a local or international laboratory.

The US-EPA Microbial Risk Assessment guidance (section 3.7 and 3.8) provides useful information on identity and microbial detection methods (US-EPA, 2012). Furthermore, guidance on how new isolates of Baculovirus species can be evaluated has been published by the EU (SANCO/0253/2008_rev.2; see list of references for link to website).

For those agents of which the identity is not confirmed and or contaminating microorganisms and metabolites are not quantified authorisation will not be granted.

For those agents of which the identity is confirmed and contaminating microorganisms and metabolites are quantified, proceed to step 2 in Figure 4.

2. Relation to human pathogens and infectiveness

If one or more species of the genus of the active and/or, where relevant, contaminating microorganisms are known to be pathogenic to humans, animals, plants or other non-target species, this should be indicated in the dossier, as well as the type of disease they cause.

It must be stated whether it is possible, and if so by which means, to clearly distinguish the active microorganism from the pathogenic species. When appropriate, particularly with regard to detection techniques, reference can be made to sections on identification and quality control. It is advised to consult appropriate scientific literature on related pathogens.

More background information and useful guidance is found in the US-EPA Microbial Risk Assessment guidance (US-EPA, 2012). The following methods may be used to identify human, animal or plant pathogens:

Taxonomy mapping

Taxonomy¹² mapping and/or phylogenetic¹³ analysis can be used to identify whether any strains and species taxonomically related to the active microorganism is known to cause infection and pathogenicity in humans. Clinical case reports and epidemiological studies can be considered. For contaminating microorganisms the procedure of OECD (2011) can be followed. The criteria for species demarcation differ for the different types of microorganism. For example, for bacteria Bergey's Manual of Systematic Bacteriology (Bergey's manual ® of systematic bacteriology, 2012) can be used and for viruses the International Committee on Virus Taxonomy provides information¹⁴. Mostly, information on species demarcation criteria relevant for a specific microorganisms is present in recent review publications on the microorganism.

Tier 1 tests and literature research

The applicant should provide information on the infectiveness of the microorganism, including information on the growth of the specific strain at different temperatures in the dossier.

¹¹ A contaminant is defined as an unintentional microbial ingredient that occurs during manufacturing.

¹² Taxonomy: the science of classification of organisms.

¹³ Phylogeny: the evolution of a genetically related group of organisms.

¹⁴ <https://talk.ictvonline.org/> (Website last entered 4 November 2019).

The applicant should provide information on the microorganism's resistance or sensitivity to antibiotics or other antimicrobial agents. Information on the stability, in terms of genetic transfer, is of particular interest if these genes are carried on mobile genetic elements, since this may be of medical relevance.

Expert judgment may be required to decide whether the MPCA is likely to be pathogenic or infective.

If the MCPA is known or likely to be a human pathogen, or may infect humans, no authorization for use will be provided.

3. Identification of metabolites of potential concern¹⁵

As a next step it should be determined if the microorganism is expected to produce metabolites of potential concern for humans and/or the environment. Information on the ability of a microorganism to produce a metabolite of potential concern for humans and/or the environment can be deduced for example from:

- a. Presence of relevant metabolites in the MPCA and/or MPCP;
- b. (eco)Toxicity studies (either guideline studies or information from published scientific literature);
- c. Information, e.g. in published scientific literature, on:
 - Biological properties of the microorganism;
 - Relationship to known plant, animal or human pathogens and the potential of related species and strains to produce relevant metabolites/toxin¹⁶;
 - Mode of action (MoA).

When on the basis of this information metabolites of potential concern for humans and/or the environment are identified, the expected exposure of humans and the environment of these metabolites of potential concern must be assessed (step 4 in Figure 4).

Exposure may consist both of the concentration of the metabolite of potential concern in the product, as well as the *in situ* production of the metabolite of potential concern in the environment. Note that as the exposure may be different for humans or the environment, the relevance of a particular metabolite can also differ per aspect; for example a metabolite that is relevant for the ecotoxicological assessment may not be relevant for the assessment of human toxicology.

Currently there is no EU harmonization on the issue of metabolites of potential concern.

A practical way forward is to work with the information that is available and assess only the risks of those metabolites for which there is an indication for a concern. An exception are active ingredients in a pest control product that are a metabolite which is present in the product at the time of application (e.g., abamectine, Bt toxin and spinosad are microbial metabolites). The human and environmental risks of such metabolites which are present in the product at the time of application should always be assessed.

4. Qualitative and quantitative risk assessment for metabolites of potential concern

A. Consumer (dietary) risk assessment for metabolites of potential concern of MPCAs

The consumer (dietary) risk assessment for microorganism is generally qualitative, i.e. if toxicity, infectivity and pathogenicity were not observed, no dietary risk assessment for the microorganism is needed.

¹⁵ The text of this section is partly based on the evaluation manual for biopesticides from the Dutch Board for the Authorisation of plant protection products and biocides (Ctgb, 2018).

¹⁶ It is proposed that if other strains belonging to the same microbial species as the strain applied for are known to produce relevant metabolites with unacceptable effect to human health and/or the environment, the nature and structure of this substance, its presence inside or outside the cell and its stability, its mode of action (MoA) (including external and internal factors of the microorganism necessary to action) as well as its effect on humans, animals or other non-target species should be provided. However, if it can be proven that the microorganism for approval does not have the genes to produce these metabolites, no additional information on these metabolites should be needed.

The risk assessment for metabolites of microorganism that are of potential concern could be qualitative or quantitative¹⁷. If a metabolite is likely to be toxic, a dietary risk assessment should be conducted.

A qualitative risk assessments can be done for metabolites produced by the microorganism once located on the crop (in situ production of metabolites). Quantifying the exposure of in situ produced metabolites is very difficult as this is influenced by a set of temporal and spatial variable environmental factors such as climate, microbiome, crop type etc. However, based on the information available an attempt can be made to build an argumentation for negligible exposure.

The quantitative risk assessment is generally only done for metabolites of potential concern that are present in the product and for which in situ production is considered to be negligible compared to the levels in the product.

For the quantitative dietary risk assessment of metabolites of potential concern present in the microbial product a tiered approach is applicable. The first tier is a simple quantitative dietary risk assessment that is described in the following section. This simple method involves the comparison of exposure levels to specific reference values (ADI, ARfD) or the Threshold of Toxic Concern (TCC) value.

The second tier proposed is the procedure for the dietary risk assessment as used for the evaluation of chemical pesticides (Chapter 5).

Tier 1 procedure for quantitative dietary risk assessment for metabolites of potential concern

The procedure described below can be regarded as a first tier because it will result in from a regulatory point of view conservative estimates of the risks for consumers of commodities treated with the microbial agent and its metabolites of potential concern. This is mainly due to the assumption of 100% persistency.

As a first step the maximum exposure of the metabolite of potential concern is calculated. This is done according:

$$Res_{max} = \frac{\sum_{i=1}^n Rate_{app}}{Y} \quad \text{Eq. 1}$$

Where Res_{max} (μg metabolite kg^{-1} crop) is the maximum residue of the metabolite of potential concern possible as result of applying a microbial agents according the intended use specified on the label (particularly application rate and number of applications), $Rate_{app}$ (μg agent m^{-2}) is the application rate of a single application and Y (kg crop m^{-2}) is the crop yield.

Crop yield data can amongst others be retrieved from FAOSTAT (2019). Selections can be made on country/regions, crops and years.

As a second step two checks are recommended.

1. the maximum exposure calculated according Eq. 1 is compared the Maximum Residue Level and
2. based on the TTC value and the exposure it is calculated how much crop (weight in kg) a person should eat on a daily basis to exceed the TTC value of the metabolite of potential considered. It can then be judged whether eating the amount of crop calculated is plausible given the diet in Kenya. The associated calculation procedure is as follows:

$$Q_{crop} = \frac{TTC}{Res_{max}} \quad \text{Eq. 2}$$

¹⁷ In quantitative assessments, the risk is expressed as a mathematical statement of the probability of illness or death after exposure to a specific hazard, and it represents the cumulative probabilities of certain events happening and the uncertainty associated with those events. Conversely, qualitative risk assessments use verbal descriptors of risk, severity, and uncertainty, and often involve the aggregation of assumptions. Source: US-EPA : <https://www.epa.gov/sites/production/files/2013-09/documents/mra-guideline-final.pdf> (last entered 18 November 2019).

where:

Q_{crop} ($\text{kg crop kg}^{-1} \text{ BW d}^{-1}$) is the quantity of crop that a person of 60 kg should eat on a daily basis to exceed the TTC value of the metabolite of potential concern evaluated; TTC ($\mu\text{g metabolite kg}^{-1} \text{ BW d}^{-1}$) is the Threshold of Toxic Concern.

TTC values for genotoxicity are usually retrieved from open literature. Res_{max} is the maximum residue calculated in equation 1.

For metabolites considered to be of genotoxic concern, either because no information on genotoxicity is available or when there is an indication that the metabolite might be genotoxic (QSAR alert, genotoxicity studies), the TTC value of $0.0025 \mu\text{g/kg bw/day}$ should be applied. When genotoxicity can be excluded for the metabolite, a TTC value for general toxicity can be applied. This TTC value is $1.5 \mu\text{g/kg bw/day}$ (Cramer Class III and Cramer Class II).

Tier 2 procedure for quantitative dietary risk assessment for metabolites of potential concern

The second tier proposed is the procedure for the dietary risk assessment as used for the evaluation of chemical pesticides (Chapter 5).

If the dietary risks of metabolites are not acceptable, the MPCA will not be authorized for use.

B. Occupational risk assessment for metabolites of potential concern of MPCAs

The occupational risk assessment for microorganism is generally qualitative, i.e. if toxicity, infectivity and pathogenicity were not observed, no occupational risk assessment for the microorganism is needed.

A qualitative risk assessments can be done for in situ produced metabolites.

A quantitative risk assessment is generally only done for metabolites of potential concern that are present in the product.

Occupational (quantitative) risk assessment for metabolites of potential concern present in the product

The method for the quantitative occupational risk assessment involves the comparison of exposure levels to specific reference values (AOEL) or the Threshold of Toxic Concern (TTC) value. For such a comparison the exposure level of the metabolite of potential concern is calculated using the EFSA AOEM model or the Croplife OPEX model. This is only possible if the level of the metabolite of potential concern in the product ($\text{mg metabolite/kg product}$) is known. If the exposure level calculated with the EFSA AOEM model or the Croplife OPEX model exceeds the TTC then risks are considered to be unacceptable.

Please note the following:

In the EFSA AOEM model, low application rates result in an overestimation of the exposure following manual spraying, since the underlying database is very limited. The following approach is proposed: For metabolites of potential concern which are present in the product, the level in the product is known (often expressed in mg/kg product). In the model the application rate of the MPCA is entered for evaluation. The results obtained in the model are then corrected for the amount of metabolite present in the product. This results in an exposure value for the metabolite, which can be compared to the reference value (AOEL) or a TTC value. For manual spray application in the field, the Croplife OPEX model would be better fitted (contains more underlying data). Therefore, the EFSA AOEM model is used as a first tier. If manual spray application results indicate an exceedance of the reference value (AOEL/TTC), then the Croplife OPEX model can be used as a refinement.

C. Environmental hazard assessment for metabolites of potential concern of MPCAs

If toxicity, infectivity and pathogenicity were not observed, no environmental risk assessment for the microorganism itself is needed. However, metabolites of potential concern need to be assessed.

It is normally not necessary to evaluate the environmental risk of potentially very low risk products, like microbial agents and their by-products, in a more elaborated way than recommended for the

conventional chemical pesticide products. Hazard identification according the US-EPA test guidelines¹⁸ will therefore be used as a first tier for the assessment of metabolites of potential concern of a MPCA.

The US-EPA test guidelines do not require dose-response testing in the first tier level, but instead a maximum hazard dose is tested, which is based on a safety factor times the maximum predicted environmental exposure. When the test shows no effect on the tested non-target organisms and plants then this is considered as sufficient prove that metabolite of potential concern or the MPCA itself do not pose unacceptable risks to the environment. Note that hazards arising from the in situ production of metabolites need to be assessed separately, as the conditions during the ecotoxicological tests may prevent the formation of metabolites by the microorganism.

Tests must be performed unless it can be justified that non-target organisms will not be exposed to the metabolite of potential concern. When according to the applicant a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

¹⁸ <https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-885-microbial-pesticide-test-guidelines> (Website last entered 8 November 2019).

5 Evaluation of chemical pest control agents – human health risk assessment

5.1 Introduction

This section provides guidance on the assessment of the risk of active ingredients/agents in pest control products on human health (occupational and consumer).

Human health risk assessment

Toxicity is an inherent property of all substances. All chemical substances can produce health effects at some level of exposure. Risk is the likelihood that an adverse health effect will result from an exposure to a particular amount (dose) of a chemical. Therefore, risk is a function of both toxicity and exposure.

The human health risk assessment process can best be described as a 3 step procedure: hazard assessment, exposure assessment, and risk characterisation.

- **Step 1 - Hazard assessment**

Examines whether a substance has the potential to cause harm to humans, and identifies the dose-response and the lowest relevant No Observed (Adverse) Effect Level (NO(A)EL)

- **Step 2 - Exposure Assessment**

Examines what is known about the frequency, timing, and levels of exposure to a substance

- **Step 3 - Risk Characterization**

Examines how well the data support conclusions about the nature and extent of the risk from exposure to pesticides.

Risk characterization is the final step in assessing human health risks resulting from exposure to pest control products. It is the process of combining the hazard, dose-response and exposure assessments to describe the overall risk posed by an active ingredient/agent in a pest control product (Figure 5). It explains the assumptions used in assessing exposure as well as the uncertainties that are built into the dose-response assessment. The strength of the overall assessment is considered, and generalized conclusions are drawn.

$RISK = HAZARD \times EXPOSURE$

This means that the risk to human health resulting from pesticide exposure depends on both the hazard (toxicity of the pesticide) and the likelihood of humans being exposed. At least some exposure and some toxicity are required to result in a risk. For example, if the pesticide is very poisonous but no people are exposed, there is no risk. Likewise, if there is ample exposure but the chemical is non-toxic, there is no risk. However, usually when pesticides are used, there is some toxicity and exposure, which results in potential risk.

Effects may vary between individuals. To account for this variability, uncertainty factors are built into the risk assessment. These uncertainty factors create an additional margin of safety for protecting individuals possibly exposed.

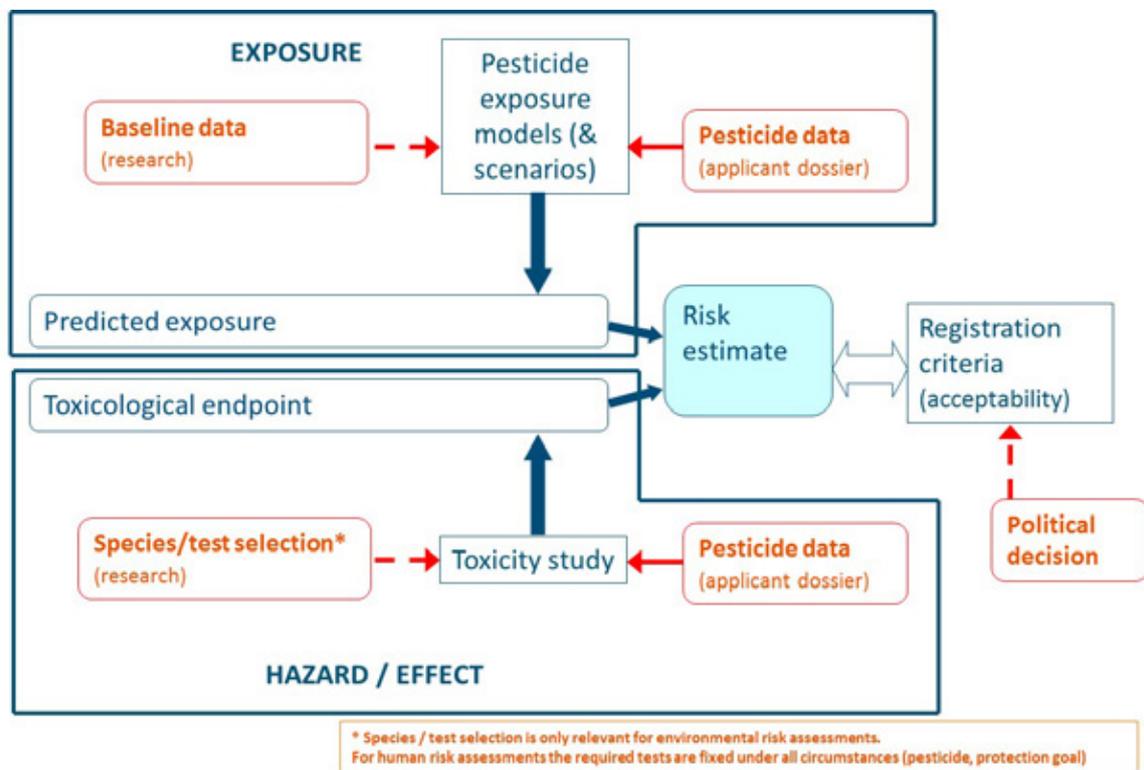


Figure 5 Risk assessment procedure.

Protection goals for human health in Kenya

Protection goals are often specified in quite general terms, e.g. stating that 'the environment' or 'human health' should be protected from risks resulting from the use of pesticides. Implementing such goals requires the specification of more precise goals for protection, usually called specific protection goals (EFSA Scientific Committee, 2016). Each specific protection goal requires definition of what should be protected, where it should be protected and how strict it should be protected.

A distinction is made between protection of users of pesticides (operators, workers), protection of residents in the vicinity of areas where pest control products are used (residents) and the protection of consumers of agricultural products that have been treated with pesticides (consumers).

The following protection goals are selected for the situation in Kenya:

- Operators
- Workers
- Residents
- Consumers (dietary)

A bystander risk assessment is not relevant to the situation in Kenya. The way a bystander is defined in EU/USA does not exist in Kenya and these persons should be considered either as operator or as resident.

The detailed protection goal for operator exposure is defined as follows:

- i. **What should be protected?**
→ All pesticide operators, i.e. all pesticide applicators, mixers and loaders.
- ii. **Where should this be protected?**
→ In all field and greenhouse crops where pesticides are applied through spraying.
- iii. **How strict should it be protected?**
→ No sub-chronic effects on the health of the operators are acceptable, i.e. no exceedance of the Acceptable Operator Exposure Level (AOEL) is allowed.

The detailed protection goal for worker exposure is defined as follows:

- i. **What should be protected?**
 - All workers, i.e. all persons entering the sprayed field for e.g. harvesting, weeding.
- ii. **Where should this be protected?**
 - In all field and greenhouse crops where pesticides are applied.
- iii. **How strict should it be protected?**
 - No sub-chronic effects on the health of the workers are acceptable, i.e. no exceedance of the Acceptable Operator Exposure Level (AOEL) is allowed.

The detailed protection goal for resident exposure is defined as follows:

- i. **What should be protected?**
 - All persons (including children) who live, work, or attend school/institution adjacent to an area treated with a pesticide; their presence is incidental and unrelated to work with pesticides and they take no action to avoid or control exposure.
- ii. **Where should this be protected?**
 - The area adjacent to an area treated with a pesticide
- iii. **How strict should it be protected?**
 - No sub-chronic effects on the health of the residents are acceptable, i.e. no exceedance of the Acceptable Operator Exposure Level (AOEL) is allowed.

The detailed protection goal for consumer exposure through food is defined as follows:

- i. **What should be protected?**
 - All consumers of agricultural commodities.
- ii. **Where should this be protected?**
 - Throughout Kenya, for all agricultural commodities that have been treated with the pesticide.
- iii. **How strict should it be protected?**
 - No acute or chronic effects on the health of the consumer, i.e. no exceedance of the Acute Reference Dose (ARfD) or the Acceptable Daily Intake (ADI) is allowed.

5.2 Framework for human health risk assessment

For Kenya different methods for human health risk assessment are worked out. These methods can be organized in a certain hierarchy: from relatively simple to more complex, and requiring an increasing amount of data. Furthermore, some methods depend on the outcome of other methods: risk assessments apply the outcome of hazard assessments. This indicative hierarchy of methods is shown in Figure 6.

First, a hazard assessment is conducted. This results in a hazard classification and in the establishment (or confirmation) of toxicological reference values (e.g. ADI, AOEL) which are needed for the risk assessments.

If the hazard assessment is concluded, it may be possible in some cases to bridge an existing risk assessment conducted by a reputable institution (see Section 5.6).

Finally, if bridging is not possible, or if it is not conclusive, the various risk assessment models can be applied, for dietary, occupational and resident risks.

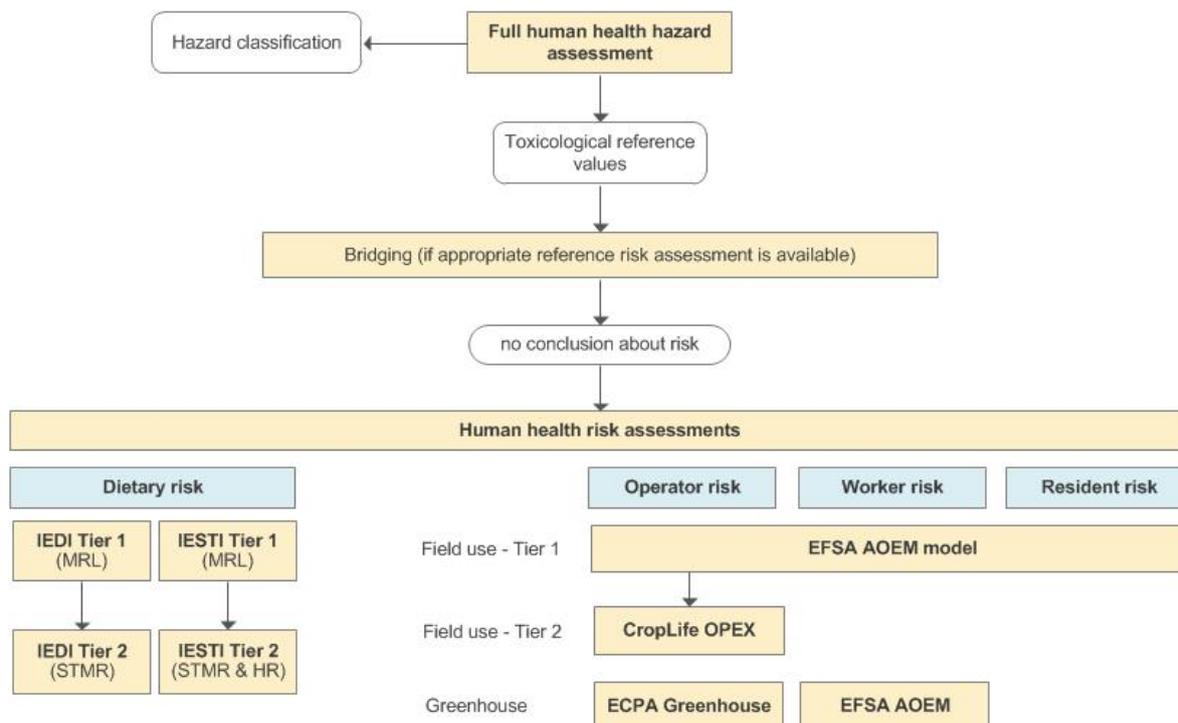


Figure 6 Evaluation flow chart for human health risk assessments as part of the framework for the evaluation of pest control product dossiers in Kenya.

5.3 Hazard assessment – Adoption of toxicological reference values

The toxicological endpoints that are derived from the submitted studies, are the basis for derivation of various reference values (ADI, AOEL and ARfD). Subsequently, these reference values are the basis of the risk assessment for the consumer, operator, worker and resident.

The reference values derived are:

- The Acceptable Daily Intake (ADI) for chronic consumer risk assessment,
- The Acute Reference Dose (ARfD) for acute consumer risk assessment
- The Acceptable Operator Exposure Level (AOEL) for the occupational risk assessment.

5.3.1 The Acceptable Daily Intake (ADI)

Consumers may be exposed to residues of plant protection products via food, throughout their life. The corresponding reference value (Acceptable daily intake, ADI) must therefore represent the dose that can be ingested over a lifetime via food without adverse health effects. The JECFA (Joint FAO/WHO Expert Committee on Food Additives) has defined the ADI as follows: 'the estimated amount of active substance, expressed per kg body weight, that can be consumed daily over a lifetime without appreciable health risks'¹⁹.

The ADI is usually derived from laboratory animal research in which the effect of prolonged exposure to the test substance has been studied, i.e. chronic toxicity research.

The following formula is used to set the ADI:

$$ADI \text{ (human dose)} = NO(A)EL(\text{experimental dose}) / 100 \text{ (default uncertainty factor)} \quad \text{Eq. 3}$$

¹⁹ Note that the US-EPA refers to the chronic reference dose (chronic RfD or RfD) instead of ADI.

The ADI is based on the most sensitive, or most critical effect. 'Effect' is defined as: an effect that is considered adverse. Usually, data on several species are available (rat and mouse and sometimes also dog). The data of the most relevant animal species for the most critical effect form the basis for derivation of the ADI. The relevance of the observed effect for man is also important. Note that more information on the NOAEL (No Observed Adverse Effect Level) is given in Annex 6.

Safety factor for calculation of the ADI

An uncertainty factor of 100 is usually applied for extrapolation of the NOAEL from laboratory animal studies to the ADI. This factor is based on a factor of 10 for differences between animal species (interspecies) and a factor of 10 for variation within the population (intraspecies). This latter factor compensates for the wider variation in sensitivity in the population of exposed workers in comparison with the relatively small (and relatively homogeneous) group of exposed laboratory animals.

Additional uncertainty factors may be used, for instance:

- when there is a discrepancy between study duration and exposure duration for which the reference value is used (e.g. the most critical effect used to derive an ADI is not from a chronic study);
- when a LOAEL was derived rather than a NOAEL;
- if there are limitations in the available toxicity data or if specific data is missing in the database for the compound.

More information can be found in chapter 5 of EFSA Scientific Opinion on default values (2012).

5.3.2 The Acute Reference Dose (ARfD)

Consumers may be exposed to residues of plant protection products via food, throughout their life. If a substance has acute toxic properties, an ARfD (Acute Reference Dose) is derived from the available toxicological studies.

The ARfD is defined as 'an estimate of the amount of a substance in food or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risks to the consumer on the basis of all known facts at the time of the evaluation' (JMPR, 2002).

The following formula is used:

$$ARfD \text{ (human dose)} = NO(A)EL \text{ (experimental dose)} / 100 \text{ (default uncertainty factor)} \quad \text{Eq. 4}$$

There is a Guidance Document of the European Commission and a JMPR Guidance on setting of acute reference dose for pesticides (EC, 2001 and JMPR, 2004). These documents provide a guideline on how the ARfD should be derived, which studies can be used as a starting point, and which effects are relevant for acute exposure.

Some substances have specific acute toxic properties or may after a short-term (single) (high) exposure induce prolonged effects. In such a situation it is possible that exceeding the ADI for a short period of time entails a health risk.

An ARfD is always derived unless the toxicological profile of the substance meets all following conditions:

- The substance induces no effects (including behaviour, clinical symptoms, or pathology) in an acute oral study at a dose level of 2000 mg/kg bw or higher.
- No embryonic, fetotoxic, or developmental effects were found at dose levels that are not maternally toxic.
- There are no indications or triggers from repeated dose studies which indicate toxic effects after acute exposure (e.g. acute neurological behaviour effects or effects on the gastrointestinal, cardiovascular or respiratory system).
- The substance shows no acute neurotoxicity or this is not expected on the basis of the available toxicological information.

-
- No other toxicological alerts such as hormonal or biochemical changes have been found in repeated dose studies which may also occur after a single dose.

As a general rule, the ARfD should be based on the most sensitive acute toxicological endpoint of human relevance, derived from the most suitable study in the most suitable (animal) species. Selection of the most relevant effect should be based on the full set of available toxicity research.

Knowledge about the mode of action of a substance may be very valuable when selecting the most relevant endpoint for acute exposure.

Some relevant effects for which an ARfD can be derived are: certain clinical effects (tremors, mucus formation/salivation), acetyl cholinesterase inhibition, delayed neuropathy, neurotoxicity, ethemoglobin formation, disturbance of oxygen transport or dissociation in mitochondria, embryonic or foetotoxic effects, developmental effects, developmental neurotoxicity, direct effects on gastrointestinal tract, pharmacological effects.

When no ARfD is derived, this should also be justified in the evaluation.

An uncertainty factor of 100 is usually applied for extrapolation of the NOAEL from laboratory animal studies to the ARfD. This factor is based on a factor of 10 for differences between animal species (interspecies) and a factor of 10 for variation within the population (intraspecies). This latter factor compensates for the wider variation in sensitivity in the population of exposed workers in comparison with the relatively small (and relatively homogeneous) group of exposed laboratory animals. Additional uncertainty factors may be used, as indicated for the ADI.

5.3.3 The Acceptable Operator Exposure Level (AOEL)

Operator exposure considered acceptable from a health point of view is in the EU referred to as AOEL (Acceptable Operator Exposure Level). The AOEL is defined as the maximum amount of a substance to which the operator (including workers in treated crops or treated spaces) can be exposed at which no adverse effects on health are expected.

The following formula is used:

$$AOEL_{systemic} [mg/kg bw/day] = (NOAEL \times Absorption) / 100 \quad \text{Eq. 5}$$

Absorption is given as the fraction of the substance absorbed by the body after oral administration, e.g. if the absorption is 60%, then the numerical factor Absorption = 0.6).

In Europe there is a Guidance Document on the setting of the AOEL (EU, 2006).

Where relevant, different AOELs can be established for acute, short-term (semi-chronic) or long-term (chronic) exposure. The AOEL is expressed in mg/kg bw/day.

Systemic AOEL/AEL

In principle, a systemic AOEL is derived. Systemic effects of active substances are caused by the amount of active substance actually absorbed into the body. In practice, exposure to these substances occurs mainly via the dermal and –to a lesser extent- via the respiratory route. For most active substances in plant protection products that are to be evaluated, however, only suitable studies with repeated exposure via the oral route are available. In practice, an AOEL is therefore usually derived on the basis of an oral study. The choice of the systemic AOEL used in the risk assessment should be justified in the decision making.

Choice of data for calculation of the systemic AOEL/AEL

The suitable studies with repeated exposure to the substance are selected from the toxicological dossier for calculation of the systemic AOEL. In addition, the kinetic data on the substance are used to establish the systemic availability (via the oral, dermal or inhalatory route) of the substance.

In principle it is assumed that the period during which exposure takes place is shorter than or equal to 3 months per year. This means that the AOEL calculation is preferably based on a short-term, i.e., semi-chronic toxicity study.

If exposure during a period longer than 3 months per year cannot be excluded based on the application scenario, a chronic toxicity study is preferred. Besides duration and frequency of exposure, the choice of the most relevant study can also be determined by the excretion rate of the active substance and its metabolites, and by the rate at which the effects that may be caused by exposure to a substance are reversible.

The most relevant studies are selected from the dossier on the basis of these considerations. The selection must be justified in the decision making.

The study with the most relevant NOAEL, obtained with the most relevant test animal, is selected. This does not necessarily always have to be the lowest NOAEL found in the most sensitive test animal. The choice of the NOAEL as starting point depends on the total package of available toxicity studies and the mutual relationships in dose regimes. The most suitable NOAEL on which the AOEL is based should be selected on a case-by-case basis, for which expert judgement is required.

Safety factor for calculation of the AOEL

A systemic AOEL is derived from the selected NOAEL by applying an uncertainty factor. In accordance with the ADI principle the uncertainty factor applied is usually 100. The basis for this approach is a factor of 10 for differences within the animal species (intraspecies differences) and a factor of 10 for differences between animal species (interspecies differences). This latter factor compensates for the wider variation in sensitivity in the population of exposed workers in comparison with the relatively small (and relatively homogeneous) group of exposed laboratory animals. Additional uncertainty factors may be used, as indicated for the ADI.

Absorption after oral exposure

Determination of the level of the systemic AOEL after oral exposure requires insight into the extent to which a substance is absorbed by the body after oral administration.

The value for absorption after oral exposure to a relevant amount of substance is the sum of the amounts of substance and metabolites that are subsequently excreted in the urine and that remain in tissues and carcass. When data are available from a study with bile-cannulated animals, the amount found in bile is often also considered as absorbed (enterohepatic circulation). If the absorbed dose is significantly lower (<80%) than the administered dose, this is adjusted by a correction factor equal to the percentage absorption. Because absorption may be dose-dependent, absorption data are required of a dose in the range of the NOAEL.

5.4 Occupational risk assessment

In this section, the occupational risk assessment including the risk assessment for residents will be described in detail. After a general introduction on hazard, exposure and risk the different models to estimate operator exposure during pesticide mixing, loading and application are described. Thereafter, it is explained how the exposure of the worker, e.g. during harvesting the crops, can be estimated. Finally, the estimation of exposure of residents is explained. Comparing the (estimated) exposure with the AOEL (hazard reference value) will result in the risk assessment.

Applicants for registration of pesticides should provide a Table of Intended Uses (also called a Good Agricultural Practice, GAP, table). To assess whether the application of a pest control products has no adverse consequences for operator and worker, the endpoints from the toxicological dossier and the corresponding reference value (e.g. AOEL) must be compared with the expected exposure.

RISK = HAZARD x EXPOSURE

Calculation of the systemic exposure

For operators and workers the dermal and inhalation routes are the most important routes of exposure. Since Good Agricultural Practice is that operators and workers should not be eating during handling the pest control product or treated crops, the oral route is not considered a relevant route of exposure for these two groups. The exposure models used will estimate the exposure on the outside of the human body, the external exposure. To compare this exposure to the AOEL, it is adjusted for route-specific absorption to calculate systemic, internal, exposure.

Uptake after dermal exposure

Insight in the extent to which the skin absorbs a substance and/or formulation after exposure to a relevant level is important for calculation of systemic exposure.

Usually the dermal absorption of a formulation is presented as a value for the concentrated formulation (used for mixing and loading) and a value for the diluted formulation (spray dilution used for application). Usually the lowest value is for the concentrated product, and the higher value is for the spray dilution.

Default values for dermal absorption as used in the EU are described in a guidance report (EFSA, 2017). Alternatively, formulation specific dermal absorption values can be used based on actual study data with the formulation or a similar formulation (acceptability criteria for comparability can also be found in the EFSA Guidance report, 2017).

Uptake after inhalation exposure

The level of systemic exposure requires insight in the extent to which a substance and/or formulation is taken up in the body via inhalation after exposure to a relevant level. A default value of 100% is applied where no suitable data on respiratory absorption at the respiratory NOAEL are available.

5.4.1 Operator risk assessment

Operator exposure is defined as the exposure of the person who applies plant protection products. Exposure of the operator can take place via the dermal route and inhalation route. It is preferably assessed on the basis of exposure studies, carried out in accordance with the current guidelines. As usually such studies are missing, first an exposure estimation is prepared with generic or more specific models. Supplementary data on actual exposure can be requested if necessary, based on this risk assessment.

There are several models available for estimation of the exposure to plant protection products.

Several parameters generally need to be filled:

- Data on the active ingredient (AOEL, oral absorption, vapour pressure)
- Data on the product (formulation type, dermal absorption)
- Data from the Good Agricultural Practice (GAP) table (application rate, frequency and interval, water volume, application technique)

5.4.1.1 Exposure models applied in Kenya

For field uses of pesticides, the EFSA AOEM model is the preferred model. A great advantage is that this model can also be used to assess other exposure groups (i.e. workers and residents) without any additional actions. However, the model does overestimate the exposure following manual spraying, since the underlying database is very limited.

For manual spray application in the field, the Croplife OPEX model would be better fitted. Therefore, the EFSA AOEM model is used as a first tier. If manual spray application results indicate an exceedance of the reference value (AOEL), then the Croplife OPEX model can be used as a refinement (see also the flow chart in Figure 6).

For greenhouse uses of pesticides, the ECPA Southern Greenhouse Model is considered the preferred model because in this model it is possible to evaluate different spraying scenarios.

5.4.1.2 EFSA AOEM Model

Explanation of the model, including scenarios and defaults

This model is the harmonised model used in Europe since 2016. The model comes with guidance (EFSA, 2014). Guidance on downloading and using the model is provided in Annex 7 and Annex 8.

Different operator exposure scenarios in the field can be assessed: tractor mounted spraying downwards or upwards, manual spraying upwards or downward using handheld spraying or knapsack spraying. In addition to the spray application of a pesticide, the model can also assess operator exposure through application of granules (broadcast application, in furrow application, manual spreading).

For the operator, different exposure results can be obtained: potential exposure considering a naked body; workwear exposure considering long-sleeved clothing is worn; workwear + PPE which can be selected (gloves, respiratory protection, closed cab).

Different default values are assumed in the model, considering an adult operator (Table 1).

Table 1 Default values applied in the EFSA AOEM model.

Parameter	Default value	Based on	Adjustable in the model?
Body weight	60 kg	Based on data from the EU; value chosen to cover a range of professionally exposed adults including teenagers and women	No
Breathing rate	1.25 m ³ /h	Average breathing rate for an operator, considering longer-term exposure	No
Average air concentration	Select based on vapour pressure active ingredient: Low volatile a.i. = vapour pressure <5*10 ⁻³ Pa Moderately volatile a.i. = vapour pressure between 5*10 ⁻³ Pa and 10 ⁻² Pa	Based on this vapour pressure of a.i., an inhalation exposure value is assumed in the model	Yes: low or moderately volatile
Exposure duration	8 hours	Based on a full working day	No
Absorption values	Oral: default 100% or look up in a.i. dossier Dermal: use default from EFSA guidance 2017 or measured value Inhalation: default 100%	Properties a.i. or default Properties product	Yes
Personal protective equipment	When PPE is selected in model, exposure values decrease based on underlying study data. In case no PPE is available in the model for the specific scenario, defaults are proposed in guidance: Gloves: 10% for liquids, 5% for solids Coverall: 10% Hood and visor: 5% Respiratory: 10-25% on inhalation depending on type		Different types PPE can be selected. Protection values by individual pieces of PPE are defined in the model.
Area treated	See next table		No

Table 2 Hectares treated per day used in the model are based on the selected crop type and spray equipment. They cannot be modified.

Crop type	Hand-held equipment ^a	Vehicle mounted equipment
Bare soil	4 / 1 ha	50 ha
Berries and other small fruit	4 / 1 ha	50 ha
Brassica vegetables	4 / 1 ha	50 ha
Bulb vegetables	4 / 1 ha	50 ha
Cane fruit	4 / 1 ha	10 ha
Cereals	4 / 1 ha	50 ha
Citrus fruit	4 / 1 ha	10 ha
Fruiting vegetables	4 / 1 ha	50 ha
Golf course turf or other sports lawns	4 / 1 ha	50 ha
Grassland and lawns	4 / 1 ha	50 ha
Grapes	4 / 1 ha	10 ha
Hops	4 / 1 ha	10 ha
Leaf vegetables and fresh herbs	4 / 1 ha	50 ha
Oil fruits (high crops)	4 / 1 ha	10 ha
Oilseeds	4 / 1 ha	50 ha
Ornamentals	4 / 1 ha	10 ha
Pome fruit	4 / 1 ha	10 ha
Root and tuber vegetables	4 / 1 ha	50 ha
Stone fruit	4 / 1 ha	10 ha
Tree nuts	4 / 1 ha	10 ha

The first value should be used for hand-held application using tank sprayers with lances; the second value for other equipment (e.g. knapsack sprayers in low or high crops).

5.4.1.3 The Croplife OPEX model

Explanation of the model, including scenarios and defaults

This spreadsheet calculator was developed by pesticide industry, but is based on exposure data from two sources: the US-EPA Pesticide Handler Exposure Database (US PHED) and the German model scenarios for handheld spray application.

The model can be downloaded through the FAO Pesticide Registration Toolkit or from CropLife International²⁰. The model includes a manual explaining how the model should be used.

The model requires input on mandatory and optional parameters; when the optional parameters are not filled in, defaults are assumed by the model. The output of the model is either expressed as Margin of Exposure (MoE) or as % of the AOEL.

Different pesticide application scenarios can be assessed:

- Aerial spraying
- Vehicle mounted spraying upwards or downwards
- Vehicle mounted spreading of granules
- Handheld spraying using backpack, hand wand or dry granule spreading

In this model not only the AOEL can be filled in, but also the underlying data: relevant NOAEL from the study, the uncertainty factor (usually 100) and the oral absorption.

The following default values are assumed in the model, considering an adult operator (Table 3).

²⁰ Toolkit : <http://www.fao.org/pesticide-registration-toolkit/tool/page/pret/assessment/a06-19-03-operator-exposure-models-and-local-risk-assessment> (last entered 18 November 2019).
CropLife: <https://croplife.org/downloads/> (last entered 18 November 2019).

Table 3 Default values applied in the CropLife OPEX model.

Parameter	Default value	Based on	Adjustable in the model?
Body weight	60 kg		Yes
Oral absorption	100%	Default (100%), or properties a.i.	Yes
Uncertainty factor	100	Standard value based on: 10 for interspecies and 10 for intraspecies	Yes
Dermal absorption	Undiluted formulation: 6% liquids and 2% for powders Diluted formulation: 30%	Based on industry evaluation; this was not accepted by EFSA (2017 guidance)	Yes
Work rate (ha/day)	Aerial: 500 ha/day Tractor downwards: 80 ha/day Tractor upwards: 15 ha/day Handheld: 1 ha/day	Practices in the USA	Yes
PPE mixing/loading	Respiratory: mask protection factor 5 (80% reduction in exposure)		No
	Dermal: Single layer long clothing: 50% reduction Coverall and long clothing (double layer): 75% reduction Chemical resistant gloves: 90% reduction		No
PPE application	Respiratory: mask protection factor 5 (80% reduction in exposure)		No
	Dermal: Single layer long clothing: 50% reduction Coverall and long clothing (double layer): 75% reduction Chemical resistant gloves: 90% reduction		No

5.4.1.4 The ECPA Southern greenhouse model

Explanation of the model, including scenarios and defaults

This model (ECPA, 2010) was developed by pesticide industry in Europe, based on studies performed in greenhouses in southern Europe (Spain, Italy). The studies were performed between 2002 and 2006 using liquid, powder and granular formulations with different active ingredients. In addition, also mixing/loading data from field studies in Greece were added. The spraying in greenhouses was performed using a spray gun connected to a large spray tank.

Based on the studies, different scenarios were included in the model:

- Upward or downward spraying (crop height either <0.5m or >0.5m)
- Standard or intensive contact with the crop (depends on space between the crop rows)

The models assumes by default that workwear (long-sleeved clothing) is worn. However, a calculation can be made assuming t-shirt and shorts.

The following default values are assumed in the model, considering an adult operator (Table 4).

Table 4 Default values applied in the Southern Greenhouse Model.

Parameter	Default value	Based on	Adjustable in the model?
Body weight	70 kg	Based on data in studies supporting the model	Yes
Inhalation absorption	100%	Default value	Yes, however, usually this worst case default of 100% is used.

All other parameters needed in the model are free variables and have to be filled in; these include:

- Active ingredient concentration (g/L or g/kg)
- Dermal absorption (concentrate and dilution, in %)
- AOEL (mg/kg bw/day)
- Application rate (kg active ingredient/ha)
- Work rate (hectares/day)

The ECPA Southern European Greenhouse model is freely accessible and is distributed by ECPA upon request²¹.

5.4.2 Worker risk assessment

A worker is a person who enters an area or handles a crop previously treated with a pesticide. For field crops, dermal exposure is assumed for the worker, whereas for greenhouse crops both the dermal and inhalation exposure routes are considered. A worker can perform different activities, crop inspection, searching/reaching and picking, harvesting, sorting and bundling (ornamentals).

Different models exist to assess worker exposure, however, these are all based on the same equation:

$$\text{Potential dermal exposure (mg a.i./day)} = TC [\text{cm}^2/\text{h}] \times T [\text{h}] \times \text{DFR} [\mu\text{g}/\text{cm}^2] \times \text{MAF} / 1000 \times \text{dermal absorption}$$

Eq. 6

Where:

TC = transfer coefficient

T = exposure time per day

DFR = dislodgeable foliar residues

MAF = Multiple Application Factor

For each of these parameters defaults are assumed based on data for each crop type. The MAF (multiple application factor) is included already in the EFSA AOEM model. For the other models, this correction for multiple applications of a pesticide has to be done outside of the model.

Different models exist to assess worker exposure: the EFSA AEM model, the EUROPOEM II model and the German re-entry model.

For the worker risk assessment, the EFSA AOEM model seems to be the most appropriate model, especially when this model is also used to assess other exposure groups. The model already has a correction incorporated for multiple applications (MAF) and can assess worker exposure in the field and in the greenhouse. In addition, this model has the option to assess potential exposure, whereas the other models assume by default long clothing is worn.

Multiple applications of a compound may cause a build-up of residue levels and must be taken into account in the exposure assessment for the estimated exposure. As long as only peak concentrations are considered in the risk assessment, residue dynamics can be expressed by a multiple application factor (MAF). The MAF is a function of the number of applications, application interval, and decline of

²¹ <https://www.ecpa.eu/contact-us> (last entered 18 November 2019).

residues, typically expressed as a DT50 assuming first order kinetics. The MAF factor is calculated using the following equation:

$$\text{MAF} = (1 - e^{-nki}) / (1 - e^{-ki}) \quad \text{Eq. 7}$$

Where,

$k = \ln(2)/\text{DT50}$ (rate constant)

$n =$ number of applications

$i =$ application interval (days)

5.4.2.1 The EFSA AOEM model

Explanation of the model, including scenarios and defaults

Different worker exposure scenarios can be assessed using this model. In the model the crop type chosen corresponds to specific worker activities. Based on the crop type selected, the model chooses which worker scenario is assessed and with what parameters.

The following worker activities are assumed in the model based on the different crop types (Table 5).

Table 5 Worker activities in the EFSA AOEM model related to crop type selected.

Crop type	Type of activity	Duration of activity (hours)
Bare soil	Not applicable	Not applicable
Fruit	(searching), reaching, picking	8
Vegetables		
Cereals	Inspection, irrigation	2
Grassland and lawns		
Hops		
Grapes	Hand harvesting	8
Golf course, sports lawn	Maintenance	8
Ornamentals	Cutting, sorting, bundling, carrying	8

As for the operator, different exposure results can also be obtained for the worker: potential exposure considering a naked body, workwear exposure considering long-sleeved clothing is worn, workwear + gloves.

The worker exposure assessment is done considering an adult worker. The following defaults are assumed in the model (Table 6).

Table 6 Default values applied for worker exposure in the EFSA AOEM model.

Parameter	Default value	Based on	Adjustable in the model?
Body weight	60 kg	Based on data from EU; value chosen to cover a range of professionally exposed adults including teenagers and women	No
Dislodgeable foliar residue (DFR)	3	Studies on different crops in EU and USA. The 90 th percentile was chosen as default value	Yes
Transfer coefficient (TC)	Depends on crop type and type of clothing/degree of protection	Studies on different crops in EU and USA.	No
Duration of exposure	2h or 8h Depends on crop type chosen in model	Full working day (8h) or realistic worst-case duration for inspection activities.	No
Multiple application factor (MAF)	Depends on number of applications, interval between applications and half-life of the active ingredient.	Standard equation	No

5.4.3 Resident risk assessment

A resident is a person who lives, works, or attends school/institution adjacent to an area treated with a pesticide. The presence of a resident is incidental and unrelated to the work with the pesticide. The resident does not take action to avoid or control exposure. The exposure of a resident is long-term.

In the EFSA AEOM model, the resident risk assessment (children and adults) can be performed. If this model is already used to assess other exposure groups, no additional actions have to be taken to perform a resident assessment.

5.4.3.1 The EFSA AOEM Model

Four different exposure routes are included in the EFSA AOEM model for the resident:

1. Spray drift during application (dermal and inhalation exposure);
2. Vapour after the pesticide has been applied (inhalation);
3. Surface deposits (dermal, for children also oral exposure);
4. Entry into treated crops (dermal, for children also oral exposure).

To estimate resident exposure, all four routes are summed, as it cannot be excluded that a resident is exposed over time through all these routes.

Different default values are assumed in the model for the resident risk assessment (Table 7).

Table 7 Default values applied for resident exposure in the EFSA OPEX model.

Parameter	Default value	Based on	Adjustable in the model?
Body weight	60 kg adult 10 kg child	Based on data from EU; value chosen to cover a range of professionally exposed adults including teenagers and women. Child: worst case for children up to 11 years old exposed as resident	No
Dermal and inhalation exposures (mL spray/person)	Depend on type of spray application and distance from spraying (buffer strip)	BREAM data and studies by Lloyd and Bell 1983 and Lloyd <i>et al.</i> 1987 Both measured drift values for different types of spray applications in different crops. Measurements performed in EU.	No
Vapour concentration	Defaults based on vapour pressure active ingredient		No
Turf transferable residues (TTR)	1% or 5% (depends on product type, liquid/granule)	Modified Californian Roller Method (Fuller <i>et al</i> 2001, Rosenheck <i>et al</i> 2001)	No
Transfer coefficient (TR)	Adult: 7300 cm ² /h Child: 2600 cm ² /h		No
Exposure duration	Dermal exposure: 2h Inhalation exposure: 24h Entry treated crops: 15 min		No
Dermal absorption	Default or measured value	EFSA 2017 guidance document	Yes
Saliva extraction factor (%)	50%	US EPA 2001	No
Surface area hands	20 cm ²	US EPA 2001	No
Frequency hand-mouth	9.5 events per hour	US EPA 2001	No
Oral absorption	Active ingredient data	Active ingredient dossier	Yes

5.5 Consumer risk assessment

5.5.1 Introduction

Persons can be exposed to pest control products by consuming treated food and drinking water that has been contaminated with (residues) of pest control products. In this section the assessment of residues in consumable crops and the assessment of consumer risk will be described in detail.

Consumer exposure is assessed by establishing which consumers will be exposed and, subsequently comparing the magnitude of exposure to a toxicological reference value.

Hazard

Based on the active ingredient dossier, toxicological reference values are derived. For the dietary risk assessment, the acceptable daily intake (ADI) and acute reference dose (ARfD, only derived if considered necessary) are relevant.

Exposure

To determine the exposure to pesticide residues through the diet, different parameters are considered relevant:

1. Residue definition

The remaining parts of a pesticide after application on crops, according to a certain use, is the residue. This can be the parent compound and/or one or more metabolites. A residue definition is determined for the estimation of dietary intake and a – sometimes different – definition is determined for enforcement/monitoring.

2. Level of residues

Each crop has a legally allowed level for each active ingredient (MRL, maximum residue limit²²). This value is based on residue trials (performed according to OECD guidelines 509).

Besides performing a risk assessment based on MRLs, more specific values can be used based on residue trials, which are the STMR (supervised trial median residue) and/or HR (highest residue).

3. Food basket

Combination of food items consumed by someone in a certain period of time.

WHO-GEMS has defined 17 diets for different regions in the world, including one for East-Africa (cluster diet 13).

More background information on the residue definition and MRLs can be found in Annex 13.

Risk assessment

Two types of consumer risk assessment can be performed: a chronic consumer risk assessment and an acute consumer risk assessment.

A chronic risk assessment assesses life-long exposure by considering mean dietary intakes and uses the ADI as reference value. For a chronic consumer risk assessment, intakes from all food items on which the pesticide is authorized (both existing registrations and the newly applied uses) are considered.

An acute consumer risk assessment is only performed when an acute reference value (ARfD) is estimated for that active ingredient. In an acute consumer risk assessment, the assumption is the consumption of a large portion, while variation in residue levels are considered. For the acute risk assessment a large portion of food is considered for each food item separately, and only the uses are assessed for which a registration has been applied for.

²² The Codex Alimentarius defines the MRL as the maximum residue limit; the EU defines the MRL as maximum residue level.

5.5.2 Chronic dietary risk assessment

For the chronic consumer risk assessment the FAO IEDI (international estimated dietary intake) model is used. At the moment, this model includes dietary information from around the world. Seventeen cluster diets have been defined, including a diet for East-Africa (cluster diet 13). The reference value (ADI) and residue levels for different food items have to be entered into the model. The model then calculates total exposure from residues on these food items combined and compares this to the reference value. The outcome is given as % of the ADI. When the exposure is below or equal to the ADI, no unacceptable risk is expected for the consumer. A step by step guidance on the use of the IEDI model is provided in Annex 12.

For chronic risk assessment, all representative uses of the active ingredient/agent of the pest control product evaluated should be taken into account. This means that if there are more products with the same active ingredient/agent already authorised, the table of intended uses/GAP table of these products should be included in the assessment as well.

Approach applied for Kenya

A tiered approach is used for the residue levels to be entered into the model:

As a first tier, the MRLs are used. This is the maximum level of residue for a specific active ingredient on a specific food item. Based on known uses of the active ingredient the residue level is expected to be lower, so using the MRL is worst case.

In case the ADI is exceeded, a refinement is made by using more specific residue levels. These are STMR values (supervised trial median residues) based on residue trials performed with the active ingredient in the crop. In this case, residue trials are needed, either performed in Kenya or bridging of existing trials may be possible (e.g. from JMPR or EFSA).

5.5.3 Acute dietary risk assessment

For the acute consumer risk assessment, the FAO IESTI (international estimated short-term intake) model is used. An acute risk assessment is only necessary when an ARfD (acute reference dose) is derived for the active ingredient. In this model, a risk assessment is performed for each food commodity and compound combination, with the outcome given as percentage (%) of the ARfD.

The model includes consumption data of large portions of food commodities from 14 countries (Australia, France, Germany, Denmark, Finland, The Netherlands, Japan, China, South Africa, Thailand, Brazil, UK and USA).

Within the FAO IESTI model, different groups of consumers can be assessed: adults in general or specifically for women and for children.

A step by step guidance on the use of the IESTI model is provided in Annex 11.

Approach applied for Kenya

For the acute consumer risk assessment a tiered approach is also applied for entering residue levels: As a first tier the MRLs are used. This is the maximum level of residue and is thus worst case.

In case the ARfD is exceeded, a refinement is made using STMR (supervised trial median residue) and HR (highest residue) values. These values are based on residue trials performed with the specific active ingredient in that crop. Residue trials are needed to obtain these values, either from Kenya or, alternatively, the possibility of bridging can be explored (for instance from JMPR or EFSA). In the latter case, GAP tables should then be compared to determine if bridging is possible.

5.6 Bridging human health risk assessments

Bridging of a pesticide risk assessment is done when an existing risk assessment conducted by a reputable body (generally a pesticide registration authority or an international organization) is reviewed and then compared to a local situation. Subsequently, a conclusion is drawn about the risk in the local situation. The existing risk assessment is referred to as the 'reference assessment' which is bridged to the conditions of use in the 'local situation', in this case Kenya.

Bridging does not require a full-fledged assessment of toxicity data and detailed local exposure estimations. Rather, it makes optimal use of work conducted by reputable evaluators with more resources. However, bridging does require good knowledge of the principles and methods of risk assessment, to be able to interpret the reference risk assessment and assess its relevance to the local situation under review.

Bridging can only be done for pesticides containing the same active ingredient (a.i.) in the reference assessment and in the local situation. Furthermore, the pesticide products (a.i. concentration and formulation) should not diverge so much that the particular risk which is being bridged will be greatly influenced. However, products do not need to be identical for bridging of risks to be possible.

The main steps in bridging a human health risk assessment are:

1. Compare the toxicology between the two situations
2. Compare the exposure between the two situations
3. Then, conclude whether the risk in the local situation is similar, lower or higher
4. Compare the risk mitigation measures between the two situations
5. Evaluate whether a conclusion about the acceptability of the pesticide in the local situation can be drawn.

When bridging an occupational risk assessment, the key toxicological parameters are the AOEL and the dermal absorption factor of the pesticide. For dietary risk assessment, the toxicological reference value is the ADI. In principle, these can be expected to be identical, or very similar across regions in the world. So the toxicology between a reference risk assessment and the situation in Kenya are generally comparable.

Occupational or dietary exposure, on the other hand, are very likely to be different between the situation in the Kenya and a reference country. So, how a reference risk assessment can be bridged to the Kenyan situation depends largely on differences in exposure.

Key parameters influencing operator exposure are:

- Application method & equipment
- Dose rate (g a.i./ha)
- Application volume (L/ha)
- Duration of application (hours/day)
- Work rate (ha/day)
- PPE during mixing & loading
- PPE during application
- Adherence to PPE rotation schedule
- Level of training/experience of the operator

Key parameters influencing worker exposure are:

- Dose rate (g a.i./ha)
- Crop type
- Duration of work in field (hours/day)
- Type of activity (e.g. crop inspection, harvesting)
- Number and interval between treatments
- Re-entry period
- PPE during work

Key parameters influencing dietary exposure are:

- Diet
- Number and type of commodities treated with the pesticide
- MRLs or actually measured residue levels (STMRs or HRs)

When the exposure in the reference and local situation have been compared, and assuming that toxicology can be considered similar in the two situations, outcomes of the bridging assessment are described in Figure 7.

More detailed guidance on bridging of risk assessments is provided the FAO Pesticide Registration Toolkit ²³. Specific guidance and assessment tables can also be found in the Toolkit, for bridging an operator risk assessment ²⁴ or a worker risk assessment ²⁵.

Assume that toxicology is similar in the two situations:		Reference country risk assessment	
		Risk considered acceptable	Risk considered unacceptable
Local exposure situation	Exposure less than reference assessment	Risk acceptable for local situation	Conduct local risk assessment
	Exposure similar to reference assessment	Risk acceptable for local situation	Risk not acceptable in local situation, without additional risk mitigation
	Exposure more than reference assessment	Conduct local risk assessment	Risk not acceptable in local situation

Figure 7 Outcome of bridging a human health risk assessment, assuming that the toxicology (hazard) of the product is similar in the reference and local situation.

²³ General bridging guidance: <http://www.fao.org/pesticide-registration-toolkit/registration-tools/assessment-methods/general-guidance-on-bridging-of-pesticide-risk-assessments-introduction-and-principles/en/> (Website last entered: 3 November 2019).

²⁴ <http://www.fao.org/pesticide-registration-toolkit/registration-tools/assessment-methods/method-detail/en/c/1187028/> (Website last entered: 3 November 2019).

²⁵ <http://www.fao.org/pesticide-registration-toolkit/registration-tools/assessment-methods/method-detail/en/c/1187109/> (Website last entered: 3 November 2019).

6 Evaluation of chemical pest control agents – environmental risk assessment

6.1 Introduction

The PCPB identified the protection of pollinators and aquatic organisms as priority.

The framework developed for the risk assessment of pollinators is described in this guidance document.

Suggestions for the development for a framework for the risk assessment of aquatic organisms is given in Ter Horst et al. (2019). The main obstacle for quickly developing such a framework is that at present local exposure cannot be estimated adequately. To do so, it is needed to develop local exposure scenarios that protect e.g. 90% of all situations in the country or the region (examples are EU: FOCUS, 2001, China: Ter Horst et al., 2014, Ethiopia: Adriaanse et al., 2014). Developing location specific exposure scenarios is time consuming and costly and preferably involves high resolution spatial and temporal data. It is advised to conduct this task in a regional context (e.g. the East African Community).

6.2 Framework for pollinator risk assessment

6.2.1 Principles of the pollinator risk assessment

The risk assessment framework for pollinators in Kenya is based on the North American approach, because its exposure estimates are considered to be robust and protective of both managed honeybees and wild bees. The North American approach is published in a guidance document (US-EPA & PMRA, 2014) and accompanied by a spreadsheet calculator, the Bee-REX model (US-EPA, 2015).

Since semi-field or field studies relevant for the Kenyan situation will very often not be available, the scheme is set up in such a way that decisions about the acceptability of risks can also be made with Tier I laboratory-generated data only, albeit with greater uncertainty.

The risk assessment approach in Kenya is based on the following protection goals:

Pollinator species to be protected

Bees are the principal pollinators of crops in Kenya and the risk assessment is therefore conducted for this group of pollinators.

The honeybee (*Apis mellifera*) is an important pollinator in Kenya. Four subspecies are present in the country, *A. m. scutellata*, *A. m. monticola*, *A. m. litorea*, and *A. m. nubica*, of which the first is the most important one.

Solitary bees are also very important pollinators in Kenya. These include Halictidae (sweat bees) that pollinate cucurbits, coffee and tomatoes, Megachilidae (leafcutter bees) that pollinate coffee and French beans, Xylocopinae (carpenter bees) that pollinate tomatoes and coffee. Stingless bees (Meliponinae) are also present throughout Kenya and known to be particularly sensitive to pesticides, but they are not managed for pollination.

This pollinator risk assessment intends to protect both **managed honeybees as well as wild bees**.

Location where bees should be protected

Hives of managed honeybee are normally not located inside a crop field but may be placed in field margins. Honeybees may forage within crops, though, if they are attractive to bees because of flowering or guttation.

Certain species of solitary bees may nest inside crop fields, especially if these are (semi-) permanent crops; many other species will breed in field margins. Therefore, pesticide **risks** to these bees will be assessed **both within-crop and off-crop**. The off-crop location will be at the edge of the treated field, which is most protective: 1 m downwind from the field for downward spray applications and 3 m downwind for upward spray applications.

Acceptable risk levels

The North American approach was developed to protect individual survival for adult bees as well as brood size and success for bee larvae.

The acceptable level of pesticide effects on Kenyan bee populations, both solitary and local honeybees, is not known at present. So it is not possible to set a percentage population reduction which is unlikely to have an impact on population size or stability, as well as on pollination function or honey production. More research is needed to establish such locally relevant threshold levels.

In the meantime, the **risk acceptability trigger values** (i.e. levels of concern: LOCs) applied in the **North American approach will also be used in Kenya**, as they are considered to be very conservative for the North American situation, and therefore expected to be protective also for many Kenyan conditions.

6.2.2 Risk assessment scheme

The overall procedure to assess the risks of pesticides to pollinators in Kenya is shown in Figure 8. It consists of four steps:

1. Assessment of potential exposure of bees to the pesticide
2. Tier-I risk assessment
3. Refined Tier-I risk assessment
4. Tier-II risk assessment

The risk assessment procedure is followed **both** for the in-crop and off-crop situations. On the basis of the outcomes of the risk assessments, risk management decisions can be made.

6.2.3 Step 1 – Probability and routes of exposure

First, it needs to be assessed whether bees can be exposed to the pesticide either in-crop and/or off-crop. This will depend on, among others, the attractiveness of the crop to bees, the timing of application of the pesticide relative to flowering, whether or not the pesticide is systemic, presence of weeds in the crop or field margins that are attractive to bees, nesting sites in or close to the crop, bee behaviour, etc.

If there is a likelihood of exposure of bees **in-crop**, either because the crop or weeds in the crop are attractive to bees, the **left-hand flow** of the scheme is followed.

If there is a likelihood of exposure of bees **off-crop** (e.g. in attractive margins of fields that are treated with the pesticide, or breeding locations close to the treated fields), the **right-hand flow** of the scheme is followed.

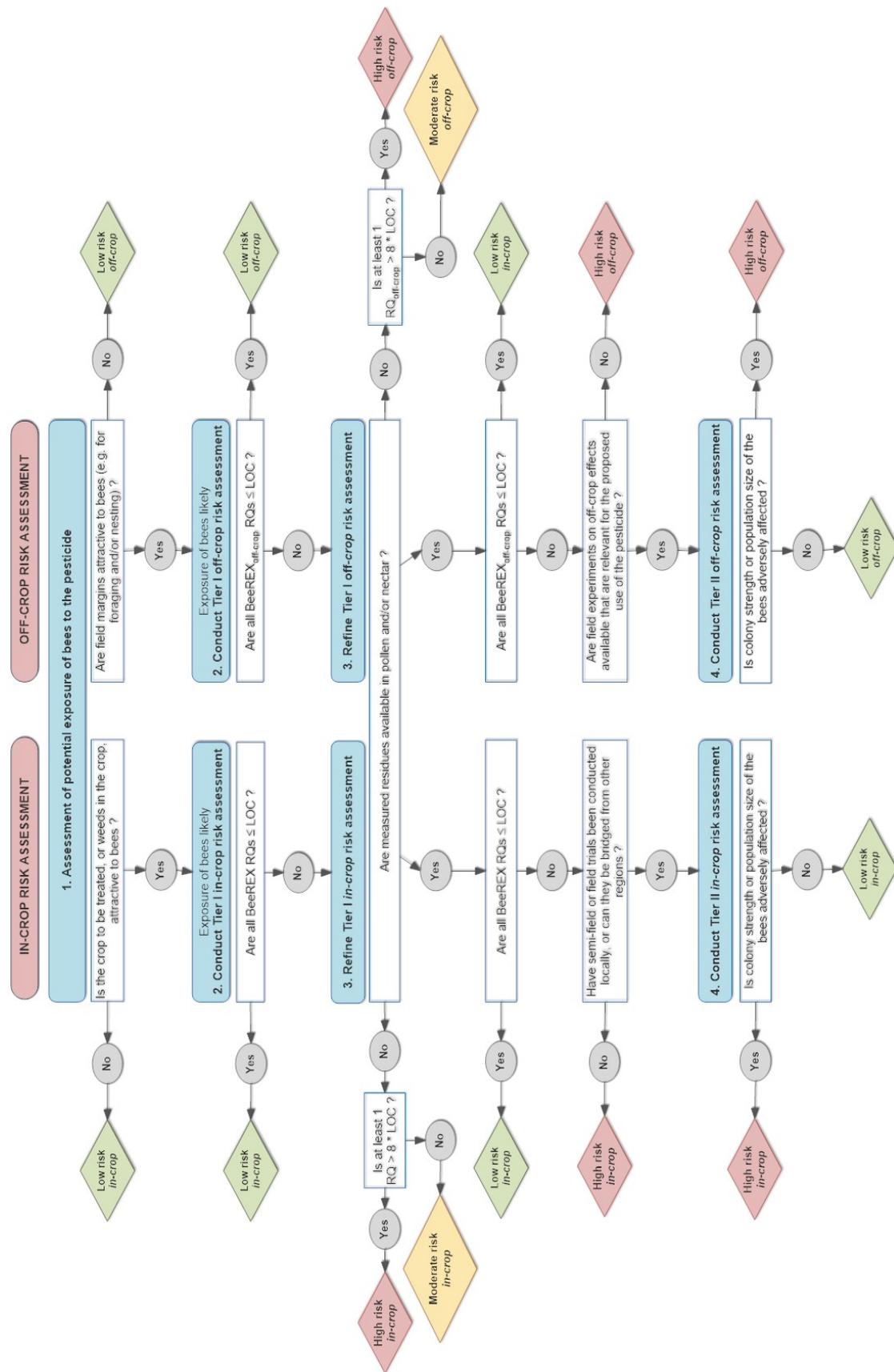


Figure 8 Evaluation flow chart for pesticide risk assessment for bees.

If bees can be exposed **both in-crop and off-crop**, **both parts of the flow chart** are followed. Note that different species may be exposed in-crop and off-crop.

If it is **unlikely** that bees will be exposed to the pesticide both in the crop and off-crop (e.g. neither the crop, nor in-crop weeds, nor field margins are attractive to bees), the risk assessment does **not need to be continued** and the pesticide can be considered low risk.

A separate risk assessment is conducted for **each crop** for which the applicant requests a registration.

6.2.4 Step 2 – Tier-I risk assessment

In step-2, a conservative risk assessment, assuming maximum exposure of the bees, is conducted using the Bee-REX spreadsheet model. For the assessment, the following risk quotients (RQs) are calculated:

- a. Acceptable risk of contact exposure of adult bees:

$$RQ = \frac{EEC_{adult\ contact}}{acute\ contact\ LD_{50}} \leq LOC$$

- b. Acceptable risk of oral exposure of adult bees:

$$RQ = \frac{EEC_{adult\ oral}}{acute\ oral\ LD_{50}\ \&\ chronic\ NOAEC} \leq LOC$$

- c. Acceptable risk of oral exposure of bee larvae:

$$RQ = \frac{EEC_{larval\ oral}}{larval\ oral\ LD_{50}\ \&\ chronic\ NOAEC} \leq LOC$$

where:

RQ = the risk quotient, which is the ratio of:

EEC = the estimated environmental concentration, to which bee adults or larvae are exposed. EEC is calculated using the Bee-REX model;

and

LD₅₀ = median lethal dose, obtained from acute laboratory toxicity studies;

or

NOAEC = No observed adverse effect concentration, obtained from chronic laboratory toxicity studies.

LOC = level of concern; value that triggers whether the risk is acceptable or not.

The pesticide is considered low risk if all RQs are less or equal to the LOC (= level of concern). If one or more RQ values are greater than the LOC, continue with step 3.

In-crop

For the in-crop Tier-I risk assessment, the input values listed in Table 8 are used in the Bee-REX model.

Table 8 Input values used in the Bee-Rex model for Tier-I assessments of the risk of pesticides to bees in Kenya. Both in-crop and off-crop inputs are provided.

Parameter	Input value			
	In-crop		Off-crop	
Exposure (EEC)				
Application rate	Maximum application rate (max-AR) requested by applicant		max-AR * drift factor (see Table 6.2-B)	
Units of app rate	Enter the right unit		Enter the right unit	
Application method	As provided in GAP-table or label		As provided in GAP-table or label	
Are empirical residue data available?	no		no	
Toxicity	Honeybees	Other (non-<i>Apis</i>) bees	Honeybees	Other (non-<i>Apis</i>) bees
Adult contact LD ₅₀	As provided in	As provided in	As provided in	As provided in
Adult oral LD ₅₀	dossier	dossier for relevant	dossier	dossier for relevant
Adult oral NOEL	(in µg/bee)	other bee species	(in µg/bee)	other bee species
Larval LD ₅₀		<i>or</i>		<i>or</i>
Larval NOEL		honeybee value/10		honeybee value/10

The application rates entered in the model are the maximum rates proposed by the applicant for each crop for which a registration is requested. For each crop, the relevant application method is selected.

Honeybee toxicity data are obtained from the registration dossier. In cases where chronic toxicity data are not available, only the acute risk assessment is conducted.

If the in-crop risk assessment is conducted for a non-*Apis* bee species, the toxicity data for the relevant species are obtained from the registration dossier. If no toxicity data are available for the relevant non-*Apis* bee species, the honeybee values can be used applying a safety factor of 10 (i.e. LD₅₀ or NOAEL non-*Apis* bee = LD₅₀ or NOAEL honeybee / 10). This safety factor is based various comparative species sensitivity studies and covers the known variability among bee species (Areana & Sgolastra, 2014; Uhl et al., 2018; Heard et al., 2016; Roessink et al. 2010).

Off-crop

For the off-crop Tier-I risk assessment, the input values listed in Table 8 are used in the Bee-REX model. The off-crop risk assessment is only done for foliar spray applications, which may drift outside the treated field. The risk of dust drift from the drilling of insecticide-coated seeds or dust formulations is not covered by this risk assessment. However, these application types are less common in Kenya.

The assessment is identical to the in-crop calculation, except that a drift factor is used to correct exposure in the field margin. Proposed drift factors are shown in Table 9. The drift factor is included in the Bee-REX model by adjusting the maximum application rate: max-AR off-crop = max-AR * drift factor.

Table 9 Drift factors for spray applications (based on EFSA, 2013 and the EU FOCUS Surface Water Step 1 and Step 2 spray drift fractions (Appendix I in FOCUS, 2001)).

Crop treated	Drift factor _{contact}	Drift factor _{diet}
Field crop – low (< 50 cm)	0.03	0.01
Field crop – high (> 50 cm)	0.08	0.03
Orchard crop – few/moderate leaves (BBCH ≤ 33) – upward spraying	0.29	0.10
Orchard crop – dense leaves (BBCH > 33) – upward spraying	0.16	0.05
Orchard crop – downward spraying (herbicides)	0.03	0.01

Note: dust drift due to mechanical drilling of treated seeds or granules is not assessed.

6.2.5 Step 3 – Refinement of Tier-I risk assessment

Measured residues are available

If measured residue values are available for pollen and/or nectar, the Tier I risk assessment can be refined by entering the measured values in the Bee-REX spreadsheet, which will override the worst case default calculation. This can be done both for the in-crop and off-crop situation (Table 10). For the off-crop situation, in case of foliar application, the empirical in-crop residue is multiplied by the relevant drift-factor. For other application types, the in-crop residue is used (worst case).

Table 10 Input values used in the Bee-Rex model for refinement of Tier-I assessments of the risk of pesticides to bees in Kenya. Both in-crop and off-crop inputs are provided.

Parameter	Input value	
	In-crop	Off-crop
Exposure (EEC)		
Are empirical residue data available?	yes	yes
Empirical residue in pollen/bread (mg a.i./kg)	as provided in the dossier	For foliar applications: = in-crop residue * drift factor (see Table 9)
Empirical residue in nectar (mg a.i./kg)	or relevant values from published literature	
Empirical residue in jelly (mg a.i./kg)		For other applications: = in-crop residue

If **all RQ values are \leq LOC**, the pesticide is considered to poses a low risk.

If **one or more RQ values are $>$ LOC**, continue with step 4.

Measured residues are not available

If no measured residues of the pesticides are available in pollen and/or nectar, Tier I cannot be refined. In principle, Tier II semi-field or full-field can then be conducted to assess whether a risk is likely to exist. However, semi-field or field studies with bees which are relevant for the local Kenyan/East African situation may not be available.

In that case, the pesticide should be considered to pose a risk to bees, based on the Tier I risk assessment. But the Tier I – not refined – risk assessment is very conservative, so that likely many pesticides will be considered to pose a risk. A distinction is therefore made in the scheme between pesticides that pose a moderate risk and those that pose a high risk, based on the degree to which the LOC is exceeded:

- A pesticide is **high risk to bees** if at least one $RQ > 8 * LOC$;
- A pesticide is **moderate risk** if $LOC < RQ \leq 8 * LOC$

The factor 8 is the ratio between hazard quotients leading to extreme hive mortality incidents and those leading to negligible bee poisoning incidents (Mineau et al., 2008). Since this ratio was based mainly on incidents with acutely toxic pesticides, care should be taken with systemic pesticides that pose a chronic risk.

6.2.6 Step 4 – Tier-II risk assessment

If a pesticide poses a risk in the Tier-I assessments, semi-field or full-field field studies can be conducted in Tier-II. These studies should preferably be done in Kenya or under cropping and environmental conditions relevant to the Kenyan situation.

Given the high cost and technical complexity of such Tier II studies, applicants should consult the PCPB to discuss their design. Kenyan bee and pollination experts will likely need to be called in to provide scientific advice.

Because the exact design of semi-field and field studies will depend on the crop, pesticide, bees to be protected and agro-environmental conditions, no single method exists on how to evaluate them. Further guidance on the design and evaluation of semi-field and field trials with bees is provided by EFSA (2013).

6.2.7 Decision making

The outcome of the above risk assessment is that the pesticide is estimated to be low, moderate or high risk to bees, either in the crop and/or off-crop, when used as recommended on a specific crop.

The possible combinations of outcomes are listed in Table 11, with for each of the combinations a suggested risk management consideration.

Risk management decisions range from allowing registration without requiring specific risk mitigation measures to refusing registration for the crop in question. In certain cases, registration may be allowed, but only if specific risk mitigation measures are taken. In the case of bee risks, precautionary phrases on the label are the most common risk mitigation measures. Such measures can only be recommended if they are realistic under the conditions of use in Kenya.

A basic premise in the decision making recommendations below is that a pesticide that is moderate or high risk to bees in the crop as well as high risk to bees off-crop should not be registered for that crop.

Table 11 Risk management considerations based on the outcome of the risk assessment for bees.

Outcome of risk assessment		Possible risk management decision	Remarks
In-crop	Off-crop		
Low risk	Low risk	No impediment to registration	Other pesticide application methods than those included in Bee-REX may pose different risks
Low risk	Moderate or high risk	Consider allowing registration with risk mitigation. Precautionary phrases on label, e.g.: <ul style="list-style-type: none"> – <i>Dangerous to bees. Do not apply when field margins are flowering</i> – <i>Dangerous to bees. Use drift reducing nozzles.</i> – <i>Dangerous to bees. Do not spray within (state distance) m from the field edge.</i> 	This outcome is not very likely to occur, except for very susceptible bee species that are active off-crop but not in-crop
Moderate risk	Low or moderate risk	Consider allowing registration with risk mitigation. Precautionary phrases on label, e.g.: <ul style="list-style-type: none"> – <i>Dangerous to bees. Do not apply on flowering crops.</i> – <i>Dangerous to bees. Remove beehives during application and for (state time) after treatment</i> – <i>Dangerous to bees. Do not apply when field margins are flowering.</i> – <i>Dangerous to bees. Use drift reducing nozzles.</i> – <i>Dangerous to bees. Do not spray within (state distance) m from the field edge.</i> 	
Moderate risk	High risk	Consider refusing registration for the crop in question	High risks for bees outside the treated field combined with moderate risks in the field are considered to be unacceptable.
High risk	Low or moderate risk	Consider allowing registration with risk mitigation. Precautionary phrases on label, e.g.: <ul style="list-style-type: none"> – <i>Very dangerous to bees. Do not apply on flowering crops.</i> – <i>Very dangerous. Remove beehives during application and for (state time) after treatment.</i> – <i>Very dangerous to bees. Do not apply when field margins are flowering.</i> – <i>Very dangerous to bees. Use drift reducing nozzles.</i> – <i>Very dangerous to bees. Do not spray within (state distance) m from the field edge.</i> 	
High risk	High risk	Consider refusing registration for the crop in question	High risks for bees both inside and outside the treated field are considered to be unacceptable.

7 Registration by equivalence

7.1 Introduction

Registration based on equivalence is conducted if the pesticide submitted for registration can be shown to be equivalent to a similar pesticide that has already been registered in the country. Two pesticides are considered equivalent if the impurity and toxicological profiles, as well as the physical and chemical properties, of the technical materials originating from different manufacturers are similar, and therefore can be expected to present similar levels of risk (FAO/WHO, 2016).

An equivalence assessment is conducted to verify whether a pest control product newly submitted for registration is equivalent to an already registered product, so that the hazards can be considered the same (or not worse) to that already registered product. As the first product has been fully evaluated, human and environmental risk assessments can be simplified or waived for a subsequent equivalent product. A confirmation of biological efficacy may be needed, however.

7.2 Equivalence evaluation of chemical pesticides

Guidance on equivalence determination found Chapter 3.2 of the Manual on development and use of FAO and WHO specifications for pesticides (FAO/WHO 2016) and its amendments²⁶ is the basis of the guidance on equivalence evaluation of chemical pesticides in Kenya. The applicant should use 'Form_A4_Generic_Pesticide_Application' which can be downloaded from the PCPB website²⁷.

Chemical equivalence applies to identical technical grade active ingredients that are manufactured after the expiry of the patent of an original/proprietary registered product. These identical products are generally referred to as generics and include conventional and biochemical pesticides.

The mandatory chemistry data requirements for the active ingredient include: physicochemical properties; manufacturing pathways; random five-batch analysis from Good Laboratory Practice (GLP) certified laboratory; methods of analysis and composition of the active substance, safener or synergist. The specification shall define the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, eco-toxicological or environmental concern within acceptable limits. The specification shall be in compliance with the relevant Food and Agriculture Organization specification as appropriate, where such specification exists. However, where necessary for reasons of protection of human or animal health or the environment, stricter specifications may be adopted. The methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, eco-toxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, shall have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.

Where technical equivalence is proven, Acceptable Daily Intake and two acute toxicological studies namely Acute oral LD50 mg/kg rat/rabbit and Acute dermal LD50 mg/kg (rat) studies specific to the technical grade material are required. Information required for four acute toxicological studies (Inhalation LC50 mg/L hour (rat), Skin irritation (rabbit), Eye irritation (rabbit) and Skin sensitization (guinea pig), Long term toxicological studies (Reproduction (specify species), Sub-chronic toxicity, Chronic toxicity, Carcinogenicity, Neurotoxicity, Teratogenicity, Mutagenicity /Genotoxicity, Metabolism

²⁶ Note that the Training Manual published by WHO and FAO contains practical examples of how to conduct an equivalence evaluation (Website: http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/eng_Participant_guide_pesticide_specification.pdf ; last entered October 3, 2019).

²⁷ The A4 applications form on generic pesticide application can be downloaded from the PCPB website: <http://www.pcpb.go.ke/application-forms/> ; last entered October 25, 2019.

(rat), Eco-toxicological studies (Birds, Fish, Daphnia, Algae, Earthworms and Soil micro-organisms), and Fate and behaviour in the environment studies may be sourced from published literature.

Where technical equivalence is not proven all the studies specific to the technical grade material must be provided.

Where an impurity is present at a concentration greater than 1 g/kg or is known or suspected to be of toxicological significance then its toxicological profile must be submitted.

7.3 Equivalence evaluation of microbial pest control agents

Annex 3 provides a simplified equivalence evaluation for MPCAs. This is the same procedure as used to assess whether a MPCA submitted for registration in Kenya is sufficiently similar to a MPCA authorized in the EU or the US.

The procedure is based on the three most critical points from a risk perspective:

- The strain is identical
- The content of relevant metabolites complies with the maximum limit set²⁸
- The content of microbial contaminants complies with the OECD issue paper (ENV/JM/MONO(2011)43; see list of references for link to website).

²⁸ Exact values of metabolite level in batches are generally not publically available. It is therefore proposed to use the maximum limit instead.

References

- Adriaanse, P.I., M.M.S. Ter Horst, B.M. Teklu, J.W. Deneer, A. Woldeamanuel and J.J.T.I. Boesten, 2015. Development of scenarios for drinking water produced from groundwater and surface water for use in the pesticide registration procedure of Ethiopia. Wageningen, Alterra Wageningen UR (University & Research centre), Alterra report 2674. (Website: <https://library.wur.nl/WebQuery/wurpubs/fulltext/346426> ; last entered September 30, 2019).
- Arena M. & Sgolastra F., 2014. A meta-analysis comparing the sensitivity of bees to pesticides. *Ecotoxicology* 23: 324– 334 (2014). (Website: <https://doi.org/10.1101/366237> ; last entered September 27, 2019).
- Codex, 2017. Description of the food category system of the Codex alimentarius. (Website: <http://www.fao.org/3/a-i5667e.pdf>; last entered September 26, 2019).
- Codex, 2019. Codex Pesticides Residues in Food Online Database. (Website: <http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/pesticides/en/> ; last entered September 30, 2019).
- Ctgb (Board for the Authorisation of plant protection products and biocides in the Netherlands), 2018, Evaluation Manual for the Authorisation of biopesticides according to Regulation (EC) No 1107/2009. Microorganisms, Botanicals and Semiochemicals version 1.1; July 2018. (Website: <https://english.ctgb.nl/plant-protection/assessment-framework/biopesticides-evaluation-manual>; last entered September 20, 2019).
- East African Community, 2019a. Regional EAC Guidelines for evaluating and reporting the efficacy of pest control products for plants. EAC secretariat Arusha, Tanzania, January 2019.
- East African Community, 2019b. Regional East African Community Guidelines for the conduct of supervised pesticide residue field trials on crops. EAC secretariat Arusha, Tanzania, January 2019.
- EC, 2018. European Commission. Commission notice concerning a list of potentially low-risk active substances approved for use in plant protection (2018/C 265/02) (Website : [https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018XC0727\(01\)&rid=7](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018XC0727(01)&rid=7) ; last entered May 15, 2019).
- EC, 2017. COMMISSION REGULATION (EU) 2017/1432 of 7 August 2017 amending Regulation (EC) No 1107/2009 of the European Parliament and the Council concerning the placing of plant protection products on the market as regards the criteria for the approval of low-risk active substances (Website : <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1432&from=EN> ; last entered May 16, 2019).
- EC, 2001. Guidance for setting of an acute reference dose (ARfD). DG SANCO E1. 7199/VI/99 rev. 5.
- ECPA, 2010. Exposure to Pesticides in the Greenhouse: A New Modeling Approach in Europe. Non-Dietary Human Exposure and Risk Assessment. Chapter 8, pp 79–94. DOI: 10.1021/bk-2010-1047.ch008.
- EFSA (European Food Safety Authority), Buist H, Craig P, Dewhurst I, Hougaard Bennekou S, Kneuer C, Machera K, Pieper C, Court Marques D, Guillot G, Ruffo F and Chiusolo A, 2017. Guidance on dermal absorption. *EFSA Journal* 2017;15(6):4873, 60 pp. (Website: <https://doi.org/10.2903/j.efsa.2017.4873> ; last entered 26 September 2019).
- EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues). 2016. Guidance on the establishment of the residue definition for dietary risk assessment. *EFSA Journal* 2016;14(12):4549, 129 pp. doi:10.2903/j.efsa.2016.4549. (Website: <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4549> ; last entered 30 September 2019).
- EFSA (European Food Safety Authority). 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. *EFSA Journal* 2014; 12(10) : 3874, 55 pp.; doi:10.2903/j.efsa.2014.3874. (Website: <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3874/abstract>; last entered 30 September 2019).
- EFSA (European Food Safety Authority). 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees). *EFSA Journal*

-
- 2013;11(7):3295, 268 pp. (Website: <https://doi.org/10.2903/j.efsa.2013.3295>; last entered 27 September 2019).
- EFSA Scientific Committee, 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. *EFSA Journal* 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579. (Website: <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2579> ; last entered 29 November 2019).
- ENV/JM/MONO(2011)43 (Website: [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2011\)43&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2011)43&doclanguage=en) ; last entered May 16, 2019).
- EU, 2019. EU Pesticide database, tab Advanced Search, type: low-risk active substance. (Website: <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN>; last entered May 15, 2019).
- EU, 2017. SANCO 7525/VI/95Rev. 10.3 13 June 2017 Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. (Website: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_guidelines_app-d.pdf ; last entered September 30, 2019).
- EU, 2006. Draft guidance for the setting and application of acceptable operator exposure levels (AOELs). (Website: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_tox_accpt-exp-levs-2006.pdf ; last entered September 25, 2019).
- EU, 1997. EU guideline 7029/VI/95 rev.5 of July 22nd, 1997, appendix B: General recommendations for the design, preparation and realization of residue trials. (Website: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_guidelines_app-b.pdf ; last entered September 30, 2019).
- FAO, 2019. FAO Pesticide Toolkit. (Website: <http://www.fao.org/pesticide-registration-toolkit/en/>; last entered May 15, 2019).
- FAO/WHO, 2016. Manual on development and use of FAO and WHO specifications for pesticides, second revision of the 1st edition, 3rd revision. FAO/WHO Joint Meeting on Pesticide Specifications (JMPS), WORLD HEALTH ORGANIZATION, FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS, Rome (Website: <http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/manual/en/> : Last entered November 2, 2019).
- FAOSTAT, 2019. FAO's Food and agriculture database (Website: <http://www.fao.org/faostat/en/#home> ; last entered May 21, 2019).
- FOCUS, 2001. 'FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC'. Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2. 245 pp.
- Bergey's manual ® of systematic bacteriology. Second edition. 2012. Springer, New York, NY. Published in 5 volumes.
- Heard, M.S., Baas J., Dorne J.L., Lahive E., Robinson A.G., Rortais A., Spurgeon D.J., Svendsen C., Hesketh H., 2016. Comparative toxicity of pesticides and environmental contaminants in bees: are honey bees a useful proxy for wild bee species? *Sci. Total Environ.*, 578 (2016), pp. 357-365. (Website: <https://doi.org/10.1016/j.scitotenv.2016.10.180> ; last entered 27 September 2019)
- JMPR, 2004. Guidance for the derivation of an acute reference dose, pesticide residues in food-2004, Report of the JMPR, FAO Plant Production and Protection Paper, 178.
- Mineau P., Harding K.M., Whiteside M., Fletcher M.R., Garthwaite D. and Knoppers L.D., 2008. Using reports of bee mortality in the field to calibrate laboratory-derived pesticide risk indices. *Environ. Entomol.* 37(2): 546 – 554
- OECD, 2007a. *Test No. 501: Metabolism in Crops*, OECD Guidelines for the Testing of Chemicals, Section 5, OECD Publishing, Paris. (Website: <https://doi.org/10.1787/9789264061835-en> ; last entered 30 September 2019).
- OECD, 2007b, *Test No 506: Stability of Pesticide Residues in Stored Commodities*, OECD Guidelines for the Testing of Chemicals, Section 5, OECD Publishing, Paris, <https://doi.org/10.1787/9789264061927-en>. (Website: https://www.oecd-ilibrary.org/environment/test-no-506-stability-of-pesticide-residues-in-stored-commodities_9789264061927-en ; last entered 30 September 2019).
- Philipp Uhl, Osarobo Awanbor, Robert S. Schulz, Carsten A. Brühl, 2018. *Osmia bicornis* is rarely an adequate regulatory surrogate species. Comparing its acute sensitivity towards multiple

-
- insecticides with regulatory *Apis mellifera* endpoints. bioRxiv 366237; (Website: doi: <https://doi.org/10.1101/366237> ; last entered September 27, 2019).
- Roessink, I., Van der Steen, J., Kasina, M., Gikungu, M., Nocelli, R., 2010. Is the European honeybee (*Apis mellifera mellifera*) a good representative for other pollinator species? (Website: https://www.researchgate.net/publication/307707875_Is_the_European_honeybee_Apis_mellifera_mellifera_a_good_representative_for_other_pollinator_species ; last entered September 27, 2019).
- Scheepmaker, J.W.A., Busschers, M., Sundh, I., Eilenberg, J., Butt, T.M., 2019. Sense and nonsense of the secondary metabolites data requirements in the EU for beneficial microbial control agents, *Biological Control*. doi: <https://doi.org/10.1016/j.biocontrol.2019.104005>
- Ter Horst, M.M.S., Wipfler, E.L., Adriaanse, P.I., Boesten, J.J.T.I., Fait, G., Li Wenjuan and Tao Chuanjiang, 2014. Chinese scenarios for groundwater leaching and aquatic exposure. Development of scenarios for environmental risk assessment procedures of pesticides in China, Wageningen, Alterra Wageningen UR (University & Research centre), Alterra report 2559. (Website: <https://edepot.wur.nl/318998> ; last entered September 30, 2019).
- Ter Horst, M.M.S., Aluoch, J.A., Barasa, M.W., Bosman-Hoefakker, S., Broeders, J., Van Etten, J., De Jong, E., Ngaruiya, P.N., Steenbergh, A., Van der Valk, H., Wagate, G., Wambugu S.M., Waswa, M.N., Wipfler, E.L. 2019. Implementation of guidance on dossier evaluation for the registration of pest control products in Kenya. Wageningen, Wageningen Environmental Research, Report 2979.
- US-EPA (United States Environmental Protection Agency). 2019a. Active Ingredients Eligible for Minimum Risk Pesticide Products. (Website: <https://www.epa.gov/minimum-risk-pesticides/active-ingredients-eligible-minimum-risk-pesticide-products>; last entered May 15, 2019).
- US-EPA (United States Environmental Protection Agency). 2019b. PART 158—DATA REQUIREMENTS FOR PESTICIDES, Subpart V—Microbial Pesticides, Source: 72 FR 61002, Oct. 26, 2007, unless otherwise noted. (Website: <https://www.ecfr.gov/cgi-bin/text-idx?SID=625a5380d90a80a00b3d73d6ff2ce023&mc=true&node=pt40.26.158&rgn=div5#sp40.26.158.v> ; last entered October 3, 2019)
- US-EPA (United States Environmental Protection Agency). 2019c. Master List of Test Guidelines for Pesticides and Toxic Substances. (Website: <https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/master-list-test-guidelines-pesticides-and-toxic> ; last entered October 3, 2019)
- US-EPA (United States Environmental Protection Agency). 2015. Bee-REX model. October 30, 2015. (Website: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#terrestrial> ; last entered September 27, 2019).
- US-EPA & PMRA EPA (United States Environmental Protection Agency & Health Canada Pest Management Regulatory Agency). 2014. Guidance for Assessing Pesticide Risks to Bees. June 19, 2014. Office of Pesticide Programs, United States Environmental Protection Agency, Washington, D.C, USA. Health Canada Pest Management Regulatory Agency, Ottawa, Canada & California Department of Pesticide Regulation, Sacramento, CA, USA. (Website: https://www.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf ; last entered September 27, 2019).
- US-EPA (United States Environmental Protection Agency). 2012. Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water. EPA/100/J-12/001. (Website: <https://www.epa.gov/sites/production/files/2013-09/documents/mra-guideline-final.pdf> ; last entered October 3, 2019).
- WHO, 2019. WHO GEMS spreadsheet for consumer risk assessment. (Website: http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/ ; last entered September 26, 2019).
- WHO, 2012. GEMS/Food consumption database. (Website: http://www.who.int/nutrition/landscape_analysis/nlis_gem_food/en/ ; last entered September 26, 2019).
- WHO, 1999. Principles for Assessment of Risk to Human Health from Exposure to Chemicals. Environmental Health Criteria no. 210. World Health Organization, Geneva.
- WHO, 1994. Environmental Health Criteria no. 170. Assessing Human Health Risks of Chemicals: Derivation of Guidance values for Health-Based Exposure Limits.

Annex 1 EU low risk criteria and US-EPA minimum risk criteria

EU low risk criteria

A set of hazard and risk based criteria are used in the EU following EU regulation 1107/2009 art. 22 and Annex II, point 5²⁹.

General

- Low-risk **products** shall not require specific risk mitigation measures, following a risk assessment

Micro-organisms

A micro-organism, in compliance with relevant data requirements, is expected to be of low risk unless:

- Adverse effects on human and animal health are documented
- Unacceptable effects on environment or non-target organisms
- At strain level it has demonstrated multiple resistance to anti-microbials used in human or veterinary medicine

Baculoviruses shall be considered as being of low-risk unless at strain level they have demonstrated adverse effects on non-target insects.

Chemical substances

Semiochemicals

A semiochemical is expected to be of low risk where the exposure (by the same route) caused by the use of the pest control product is similar (within one order of magnitude) to or lower than natural exposure levels of the semiochemical.

Physical and chemical properties

An active substance, other than a micro-organism, shall not be considered as being of low-risk where it is classified as explosive

Human health

An active substance, other than a micro-organism, shall not be considered as being of low-risk where it corresponds to at least one of the following:

- Acute toxicity category 1, 2 or 3,
- Skin corrosive, category 1A, 1B or 1C,
- Serious damage to eyes, category 1,
- Skin sensitiser category 1,
- Mutagenic category 1A, 1B or 2,
- Carcinogenic category 1A, 1B or 2,
- Toxic to reproduction category 1A, 1B or 2, or
- Specific Target Organ Toxicant, category 1 or 2,
- Respiratory sensitiser category 130,
- Endocrine disruptor or has neurotoxic and immunotoxic effects.

²⁹ <http://data.europa.eu/eli/reg/2009/1107/oj> and <https://eur-lex.europa.eu/eli/reg/2017/1432/oj> (last entered 18 November 2019).

³⁰ Since an active substance identified as a skin sensitiser can potentially induce hypersensitivity reaction, potential respiratory sensitisation should be taken into account when appropriate tests are available or when there are indications of respiratory sensitisation effects.

Environmental health and behaviour

- An active substance, other than a micro-organism, can be considered of low risk where it meets the following criteria:
 - Not persistent in soil: $DT_{50,soil}$ lower than 60 days,
 - Not leaching to groundwater through soil: predicted concentration in groundwater should be lower than 0.1 µg/L in all scenarios,
 - Not persistent in water-sediment: DT_{50} in fresh or estuarine water sediment lower than 60 days, and DT_{50} in fresh or estuarine water lower than 20 days,
 - Bioconcentration factor is lower than 1000 for substances which are readily biodegradable and 100 for substances which are not readily biodegradable,
 - Not persistent in air ($DT_{50} < 2$ days).
- An active substance, other than a micro-organism, should not be considered of low risk where it has to be classified as toxic to aquatic life of acute category 1.
- An active substance, other than a micro-organism, may be considered of low risk if the risk assessment carried out on representative product/(s) concerning acute and long-term toxicity to birds, mammals, aquatic and soil organisms, bees, non-target arthropods and non-target plants *do not require specific risk mitigation measures*.

US EPA minimum risk criteria

A minimum risk product must meet the six conditions listed below in order to be classified as minimum risk pesticides by the US EPA³¹.

- **Condition 1:** The product's active ingredients must only be those that are listed in 40 CFR 152.25(f)(1).
- **Condition 2:** The product's inert ingredients may only be those that have been classified by EPA as:
 - Listed in 40 CFR 152.25(f)(2)³²
 - commonly consumed food commodities, animal feed items, and edible fats and oils as described in 40 CFR 180.950(a), (b), and (c); and
 - certain chemical substances listed under 40 CFR 180.950(e).
- **Condition 3:** All of the ingredients (both active and inert) must be listed on the label. The active ingredient(s) must be listed by label display name and percentage by weight. Each inert ingredient must be listed by label display name.
- **Condition 4:** The product must not bear claims either to control or mitigate organisms that pose a threat to human health, or insects or rodents carrying specific diseases.
- **Condition 5:** The name of the producer or the company for whom the product was produced and the company's contact information must be displayed prominently on the product label.
- **Condition 6:** The label cannot include any false or misleading statements.

³¹ <https://www.epa.gov/minimum-risk-pesticides/conditions-minimum-risk-pesticides> (last entered 18 November 2019).

³² <https://www.epa.gov/minimum-risk-pesticides/active-ingredients-eligible-minimum-risk-pesticide-products> (last entered 18 November 2019).

Annex 2 Guidance on using the EU 'low risk active substance' list and the US-EPA 'minimum risk pesticides' list

Source: EU 'low risk active substance'

The European Union identifies low risk active substances. These are pesticides which have been evaluated in the standard manner (standard EU evaluation methods), but were identified as posing a low risk to human health and the environment. Criteria for low risk active substances have been laid down in a Commission Regulation³³. At present active substances identified as 'low risk' by the EU can be found via the EU pesticide database (EU, 2019)³⁴.

The screenshot shows the EU Pesticides database website. On the left, a 'Select criteria' filter panel is visible. The 'Type' dropdown menu is set to 'Low-risk active substance'. In the center, the 'Advanced Search' button is highlighted. On the right, a table lists active substances, with a callout box indicating that this is the list of 'low risk' active ingredients (a.i.).

Name	Status under Reg. (EC No 1107/2009)
Bacillus amyloliquefaciens strain FZD24	Approved
Cerevisiane	Approved
COS-OGA	Approved
Ferric phosphate	Approved
Isaria fumosorosea Apopka strain 97 (formerly Paecilomyces fumosoroseus)	Approved
Mild Pepino Mosaic Virus isolate VC 1	Approved
Mild Pepino Mosaic Virus isolate VX 1	Approved
Pepino mosaic virus strain CH2 isolate 1905	Approved

Figure 9 Instruction for obtaining the list of low risk active substances on the EU Pesticides database website.

In order to get the list of low risk active substances, on the website the button 'Advanced Search' should be clicked (Step 1 in **Figure 9**). Upon clicking this button a filter function appears at the left hand side of the screen. In this filter function select 'Low risk active substances' from the picklist of the 'Type' field (click the small arrow behind the white coloured field to visualize the picklist) (Step 2 in **Figure 9**). Next in the table at the right hand side of the screen the list with low risk actives

³³ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1432&from=NL> (Website last entered 4 November 2019).

³⁴ <https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN> (Website last entered 4 November 2019).

ingredients appears (Step 3 in **Figure 9**). To view details of the active substance click on the '+' next to the active substance name.

At this moment (11 October, 2019) 16 low risk pesticide active ingredients are in the EU list, and they are registered in the EU for a duration of 15 years instead of the 10 years for other pesticide active ingredients.

Source: EU potential 'low risk active substances'

Currently, the EU (Standing Committee on Plants, Animals, Food and Feed Section) is re-evaluating according Regulation EC 1107/2009 about 50 active substances that were identified as potential low-risk substances under Directive 91/414/EEC. This list of potentially low-risk active substances/agents approved for use in plant protection is published in Commission notice 2018/C 265/02 (EC, 2018).³⁵ Note, that of the about 50 substances on this list, the low risk status of sulphur is questionable due to possible risks for pollinators.

Source: US-EPA 'minimum risk pesticides'

The United States Environmental Protection Agency (US-EPA) publishes a list of active substances currently considered as 'minimum risk pesticides'. These are pesticides that pose little or no risk to human health and the environment and therefore do not need to be registered in the USA. The list of present active substances allowed in 'minimum risk pesticides' is published on the US-EPA web site (EPA, 2019a) ³⁶.

³⁵ [https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018XC0727\(01\)&rid=7](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018XC0727(01)&rid=7) (Website last entered 4 November 2019).

³⁶ <https://www.epa.gov/minimum-risk-pesticides> (Website last entered 4 November 2019).

Annex 3 Guidance on the equivalence evaluation for microbial agents for Kenya

For microbial agents a simplified equivalence evaluation is used. The procedure is based on the three most critical points from a risk perspective:

- The strain is identical
- The content of relevant metabolites complies with the maximum limit set³⁷
- The content of microbial contaminants complies with the OECD issue paper (ENV/JM/MONO(2011)43; see list of references for link to website).

i. Verify that the same strain is applied for

Indicators pointing towards that the strain of the local microbial agent for which registration is required is the same as that of the microbial agent classified as low-risk or potentially low-risk by the EU or as minimum risk pesticides by the US-EPA used as reference are:

- the applicant that requires registration for the microbial agent in Kenya is the same as the applicant of the microbial agent used as reference.
- the applicant is able provide a letter of access provided by owner of the strain (granting access to the data of the substance dossier).

ii. Verify that the content of relevant metabolites complies with the maximum limit set

- Check if a relevant metabolite has been identified and what limit has been set.
- Five batch data needs to be provided showing that the level of the metabolite in the Kenyan specification is below the maximum limit.
 - Make sure that batch data represent 5 independent batches (e.g. different production dates)
 - The comparison between the maximum limit and the level in the Kenyan specification should include the appropriate method to derive the maximum level (e.g., average level + 3 × standard deviation based on the data of the 5 batches).

iii. Verify that the content of microbial contaminants complies with the OECD issue paper

Verification starts with the question which relevant metabolites of the microbial agent used as reference have been identified. For each relevant metabolite the maximum level set needs to be retrieved.

The applicant of the local microbial agent needs to provide the five batch analysis data³⁸. It is important to confirm that the batch data represent five independent batches (e.g. different production dates). Using the five-batch data of the microbial agent for which registration is requested, as a second step, the regulator verifies that the content of the relevant metabolites identified for the reference microbial agent is acceptable for the Kenyan specification (i.e. **not** exceeding the maximum level set).

During the production of microbial pest control agents unwanted microorganisms can be produced in addition to the microbial pest control agent. Depending on the growing conditions, these unwanted or contaminating micro-organisms could include pathogens, their associated toxins and other metabolic by-products of health concern (ENV/JM/MONO(2011)43). As a result, a contaminated microbial pest control product could pose a risk if it is applied over human populated areas, habitats frequented by susceptible non-target organisms or other sensitive areas (i.e. drinking water abstraction areas) as well as to food crops up to, or near, the time of harvest (ENV/JM/MONO(2011)43). The OECD issue paper on microbial contaminants (ENV/JM/MONO(2011)43; the link the issue paper can be found in the References section of this report) provides a list of indicators indicative of pathogen presence. As the screening of pathogens themselves is not advised, the indicators can be used instead to verify presence of these unwanted or contaminating microorganisms. Some indicators for contamination mentioned in

³⁷ Exact values of metabolite level in batches are generally not publically available. It is therefore proposed to use the maximum limit instead.

³⁸ The five-batch analysis is necessary for identifying and quantifying impurities within the production batches of substances/microbial agents. The study requires the analysis of five representative production batches for the presence of significance impurities ($\geq 0.1\%$ w/w) and borderline impurities ($0.1\% > x \geq 0.06\%$) to generate the product specification for regulatory needs.

the OECD issue paper are optional, e.g. depending on region of manufacturing location, others are always required. The paper specifies different criteria for baculoviruses.

As a third step it is proposed that the regulator checks:

1. Whether the five batch analysis is done for all relevant indicators proposed in the OECD issue paper and
2. That for each individual contaminant the measurements comply with the limits set for the relevant indicator in the OECD issue paper.

Relevant information from the OECD issue paper needed for these checks are given below.

Table 1.1: Proposed OECD microbial contamination screening requirements for microbial pest control products (excluding baculoviruses manufactured in vivo)

Type of Indicator	Indicator	Limit*	Rationale
Pathogen	<i>Salmonella</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA and Health Canada requirement - many standard methods available - often used in the food industry
	<i>Listeria monocytogenes</i>	Absence in 25 g or 25mL	<ul style="list-style-type: none"> - recent health concern with respect to contaminated fruits/vegetables and processed meat products - can survive/multiply on foods stored under refrigerated temperatures - optional requirement particularly if screens for other hygiene indicators consistently demonstrate acceptably low levels of contamination. Regulatory authorities must also have a high degree of confidence in the manufacturer's quality assurance programme when deciding whether to waive routine screening for this micro-organism
	<i>Vibrio</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA test guideline requirement, therefore testing is mandatory for U.S. registration/authorization - not endemic in many countries - basic food handling precautions/personal hygiene habits exclude these organisms during manufacturing - isolation of specific species or pathogens (e.g., <i>Vibrio cholerae</i>) is NOT recommended unless the analytical laboratory follows appropriate biohazard protocols - optional requirement and recommended ONLY if there is a high potential for contamination or if species of <i>Vibrio</i> are known to naturally occur at the geographical location of the manufacturing site
	<i>Shigella</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA test guideline requirement, therefore testing is mandatory for U.S. registration/authorization - not endemic in many countries - most commonly related to undercooked shellfish rather than manufacturing processes; basic food handling precautions/personal hygiene habits exclude these organisms during manufacturing - isolation of specific species or pathogens (e.g., <i>Shigella dysenteriae</i>) is NOT recommended unless the analytical laboratory follows appropriate biohazard protocols - optional requirement and recommended ONLY if there is a high potential for contamination or if species of <i>Shigella</i> are known to naturally occur at the geographical location of the manufacturing site

Type of Indicator	Indicator	Limit*	Rationale
Microbial Activity	Aerobic Plate Count	< 10 ⁵ CFU/g or mL	<ul style="list-style-type: none"> - indicator of aerobic bacterial contamination - often used in the food industry - many standard methods available - optional requirement if MPCCA is an aerobic bacterium
	Anaerobic spore-formers	< 10 ⁵ CFU/g or mL	<ul style="list-style-type: none"> - cause of health concerns in the food industry; indicates hygiene failures during processing - anaerobic spore-forming organisms have potential to persist in soil/water for long periods of time - standard methods for anaerobic spore-formers available - optional requirement if other hygiene indicators (i.e., <i>Escherichia coli</i> and <i>Staphylococcus aureus</i>) are screened during product manufacture and if the MPCCA is a known micro-aerophile
	Yeast and Mould Count	< 1000 CFU/g or mL	<ul style="list-style-type: none"> - many standard methods available - general indication of yeast and mould contamination, and potential presence of mycotoxins - may be optional requirement if MPCCA is a fungus
Human, fecal and environmental contamination	<i>Escherichia coli</i> OR Thermotolerant (fecal) coliforms	Absence in 1 g or mL < 10 CFU/g or mL	<ul style="list-style-type: none"> - indicator of fecal contamination - recent health concern involving contaminated fruits/vegetables; certain sensitive sub-populations are particularly at risk - can survive/multiply on plants and in soil and water - many standard methods available
	<i>Staphylococcus aureus</i>	Absence in 1 g or mL	<ul style="list-style-type: none"> - indicator of contamination due to improper handling - many standard methods available
	<i>Pseudomonas aeruginosa</i>	Monitoring*	<ul style="list-style-type: none"> - indicator of environmental contamination - optional requirement recommended ONLY if screening results for other hygiene indicators suggest possible presence of pseudomonads
	Mouse IP/SC assay	No evidence of infection or injury in test animals	<ul style="list-style-type: none"> - optional requirement recommended ONLY for products where there is a significant potential for contamination by a primary mammalian pathogen, especially if closely related to the MPCCA, or when there is significant potential for production of a toxin of concern that cannot be ruled out by appropriate analysis by any other means - unnecessary if intravenous/intraperitoneal (IV/IP) toxicity and pathogenicity (infectivity) test data on the pre-formulated product shows no positive results for toxicity or if toxicity may be attributed to an ingredient other than the MPCCA
Other tests (product-by-product basis)			

* Evaluation will be based on levels that occur.

Table 1.2: Proposed OECD microbiological contamination screening requirements for baculovirus-based pest control products manufactured in vivo

Type of indicator	Indicator	Limit	Rationale
Severe pathogen	<i>Salmonella</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA and Health Canada requirement - many standard methods available - often used in the food industry
	<i>Vibrio</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA test guideline requirement, therefore testing is mandatory for U.S. registration/authorization - not endemic in many countries - basic food handling precautions/personal hygiene habits exclude these organisms during manufacturing - isolation of specific species or pathogens (e.g., <i>Vibrio cholerae</i>) is NOT recommended unless laboratory follows appropriate biohazard protocols - optional requirement and recommended ONLY if there is a high potential for contamination or if species of <i>Vibrio</i> are known to naturally occur at the geographical location of the manufacturing site
	<i>Shigella</i>	Absence in 25 g or 25 mL	<ul style="list-style-type: none"> - U.S. EPA test guideline requirement, therefore testing is mandatory for U.S. registration/authorization - not endemic in many countries - most commonly related to undercooked shellfish rather than manufacturing processes; basic food handling precautions/personal hygiene habits exclude these organisms during manufacturing - isolation of specific species or pathogens (e.g., <i>Shigella dysenteriae</i>) is NOT recommended unless laboratory follows appropriate biohazard protocols - optional requirement and recommended ONLY if there is a high potential for contamination or if species of <i>Shigella</i> are known to naturally occur at the geographical location of the manufacturing site
Moderate with limited spread	<i>Bacillus cereus</i>	10 ⁷ CFU/g or mL	- part of natural intestinal microflora of insect larvae
	<i>Staphylococcus aureus</i>	Absence in 1 g or mL	- indicator of contamination due to improper handling
Indicators of human, fecal or environmental contamination	Total coliforms	< 100 CFU/g or mL	- many standard methods available
	<i>Escherichia coli</i>	Absence in 1 g or mL	- optional requirement if host insect larvae are laboratory reared and rearing facility is able to maintain a reasonably hygienic colony where likelihood of contamination by non-fecal coliforms is low or limit for fecal coliforms/ <i>E. coli</i> is satisfied
	OR Thermotolerant (fecal)	< 10 CFU/g or mL	<ul style="list-style-type: none"> - indicator of fecal contamination - recent health concern involving contaminated fruits/vegetables; certain sensitive sub-populations are particularly at risk - can survive/multiply on plants and in soil and water

Type of indicator	Indicator	Limit	Rationale
	coliforms		- many standard methods available
	Total aerobic bacteria (mesophiles)	10 ⁸ CFU/g or mL	- indicator of aerobic bacterial contamination - often used in the food industry - many standard methods available
	Yeast and Mould Count	Visually monitored ^a	- many standard methods available - optional requirement recommended ONLY if screening results for other hygiene indicators suggest possible presence of yeasts or moulds
Other tests (case-by-case basis)	Mouse IP/SC assay	No evidence of infection or injury in test animals	- required by U.S. EPA and Health Canada if microbiological contamination at the insect rearing facility is high and not well characterized or if baculovirus is produced in such a way that there is high batch-to-batch variability and may contain unknown contaminants which may not be readily detected on microbe-specific media (e.g., baculovirus is produced in wild larvae) - optional requirement; unnecessary if intravenous/intraperitoneal (IV/IP) toxicity and pathogenicity (infectivity) test data on the pre-formulated product shows no positive results for toxicity

^a evaluation based on levels that occur

Annex 4 Guidance on registration by analogy

Theory of registration by analogy

The main steps in assessing whether registration by analogy is feasible are schematically shown in Figure 10. The use of this method is intended for low risk products.

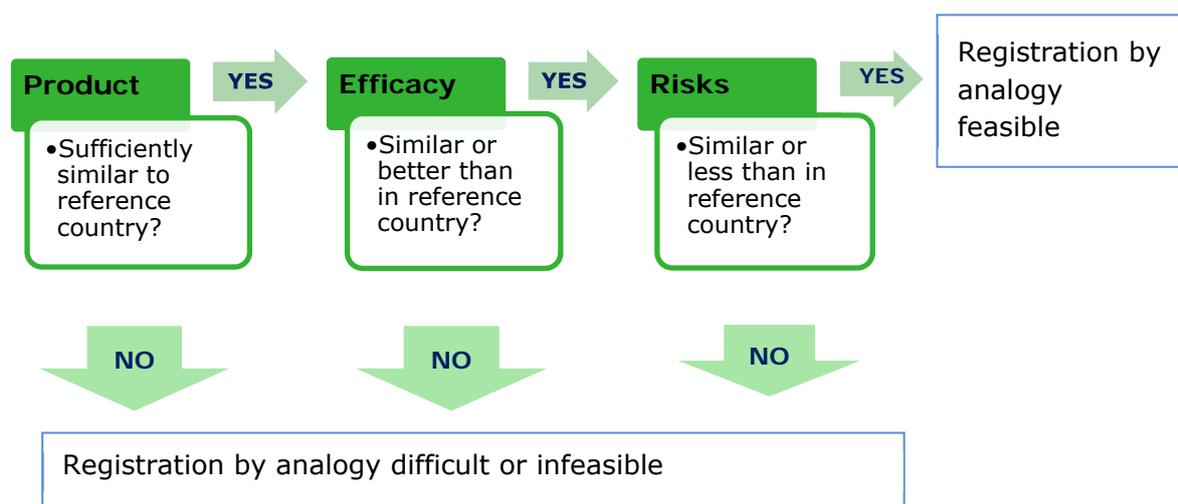


Figure 10 Registration by analogy: compare local situation with situation in reference country (source: FAO Pesticide Registration Toolkit; FAO, 2019). Note that as a first step it is evaluated whether the formulated product is sufficiently similar.

For evaluation by analogy, ideally a comparison is made between identical pest control products, from the same manufacturer. However, a full equivalence assessment is usually not possible as the reference specification is generally confidential information. For Kenya products considered sufficiently similar also qualify for registration by analogy. No specific guidance is developed to assess whether the active substance/agent of the local product is sufficiently similar to the active substance/agent classified as low-risk or potentially low-risk by the EU or as minimum risk pesticides by the US-EPA.

For products containing active substances of chemical origin (incl. botanicals and semiochemicals), the decision can be made based on:

- The minimum purity of the active substance,
- The maximum content of the relevant impurity/impurities and
- The manufacturing process (not producing other relevant impurities).

For microbial agents a simplified equivalence evaluation is given in Annex 3. The procedure is based on the three most critical points from a risk perspective:

1. The strain is identical
2. The content of relevant metabolites complies with the maximum limit set³⁹
3. The content of microbial contaminants complies with the OECD issue paper (ENV/JM/MONO(2011)43; see list of references for link to website).

³⁹ Exact values of metabolite level in batches are generally not publically available. Therefore the maximum limit is used instead.

Thereafter, the use pattern of the pest control product is compared between the reference country and the local situation. This includes the crop or use situation, pest, application rate and frequency, and withholding periods, if any. The comparison of use patterns helps to evaluate whether the efficacy in the local situation can be expected to be similar – or better – than in the reference country.

Subsequently, the potential for human health and environmental impact is compared between the reference country and the local situation. This is done by comparing use patterns again, but now the aim is to assess the likelihood of similar human or environmental exposure. Any use restrictions, personal protective equipment and environmental conditions are also taken into account. This leads to a conclusion whether the risks in the local situation can be expected to be similar, higher or less than in the reference country.

Note however, that in the EU one of the criteria for low risk is that specific risk mitigation measures are not needed to ensure acceptable risks (i.e. there are no specific risk mitigation measures specified on the product label)⁴⁰. The US-EPA has no criteria on risk mitigation options (see <https://www.epa.gov/minimum-risk-pesticides/conditions-minimum-risk-pesticides>; website last entered 11 October 2019).

The comparison of environmental exposure is very difficult due to the large number of factors that determine the exposure. For low-risk products it is advised not to spend too much efforts on this comparison of environmental exposure in the evaluation procedure.

To facilitate the registration by analogy evaluation, the FAO Pesticide Registration toolkit provides a checklist for performing registration by analogy and an associated guidance document (note that they both might be updated by the FAO. It is advised to check the FAO Pesticide Registration toolkit website to retrieve the latest versions).

For registration of MPCAs in Kenya the FAO Registration by Analogy check-list was somewhat altered to make it more suitable for microbial pest control agents. This check-list and associated guidance are provided in Annex 5 (currently the FAO Pesticide registration toolkit website does not contain such a check list for MPCAs).

Decision making based on registration by analogy

In registration by analogy, a comparison is made between i) the registered application rate and frequency of application of the pesticide, and its use restrictions or precautions, in the reference country and ii) the proposed application rate and frequency of application of the pesticide, and use conditions, in Kenya.

The likelihood that the risk in Kenya will be acceptable or not is subsequently assessed. Based on the assessment the regulator needs to indicate whether the product can be registered in Kenya.

Registration by analogy is not always applicable. For instance a proper comparison might not be possible, because there is not enough information in the dossier of the reference country. In such cases the conclusion on whether the product can be registered based on the registration by analogy approach in Kenya should be 'No'. Consequently the decision supporting flow chart will guide the regulator towards the next step: more in-depth evaluation methods making a division between pest control products of chemical origin and microbial pest control products.

⁴⁰ For MPCAs gloves are always prescribed. This is however not considered as a specific risk mitigation measure, and therefore does not prevent the low risk status. Reason from prescribing gloves for MPCAs is that there are currently no suitable tests for sensitization, therefore gloves are prescribed as a general precaution measure.

Annex 5 Registration by analogy checklist and guidance for microbial pest control products⁴¹

Guidance for completing the checklist for microbial pest control products

10. Active ingredient manufacturing source

If the source is different equivalence needs to be shown in terms of strain used. In addition, microbial contaminant that may occur during production need to be checked and batch analysis should be provided to show that the batches do not contain microbial contaminants following the OECD issue paper on microbial contaminants. See Annex 3 of this report for more detailed guidance.

11. Relevant metabolites (if identified)

If a microorganism can produce a relevant metabolite a limit may have been set in the reference country. Please indicate that the microbial pest control agent complies with this limit. See Annex 3 of this report for more detailed guidance.

12. Co-formulants triggering a hazard classification

Unless the reference product is produced by the same applicant you will not know the composition of the reference product. Comparing the two will be difficult if not impossible in those cases. In that case it is advised to use own classification and labelling.

13. Dose rate (g a.i./ha), number of applications per growing season, withholding period

To determine the critical use and integral approach is advised i.e. it is needed to simultaneously examine the dose rate, the number of applications per growing season and the withholding period

17. Conclusion with respect to the use

If the use for the local situation is different than that of the reference situation it does not necessarily mean that the product cannot be authorized as for many microorganisms a quantitative risk assessments for human exposure (both dietary and non-dietary) is not required in the EU.

18. Level of training/experience of operator

In several (reference) countries like e.g. the Netherlands professional users need to follow a training before they get a license to use professional products. However, this does not mean that the product cannot be authorized for less experienced users.

It is also possible that in (reference) countries some products are only authorized for amateur use (home/garden) since much smaller areas to be treated are assumed for this grouped compared to professional users it is not possible to extrapolate from use for amateurs only to professional use.

19. Environmental risk - Use restrictions for bees

For environmental risks it is advised to specifically examine the use restriction for bees like e.g. the restriction not to use the product in flowering crops.

⁴¹ This check list was developed using the Registration by Analogy checklist for pesticides of chemical origin of the FAO Pesticide Registration Toolkit website as basis.

Registration by analogy – check-list for microbial pest control agents

Product name:	Registration file number:
Name of the assessor:	Date of the assessment:

Comparison of parameters for the local situation under review and a reference country			
Parameter	Describe/quantify the parameter for:		Remarks
	Local situation (application)	Reference country (registration)	
Country			
1 Country			
Applicant/registrator			
2 Name and address of applicant/registrator			
3 Name of manufacturer		(usually confidential)	
4 Registration status in reference country			
Pesticide product			
5 Product name			
6 Active ingredient common name			
7 Formulation type			
8 Active ingredient concentration in the product (CFU/g or mL)			
9 Declaration by applicant that the product is sufficiently similar or identical to the one in the reference country			
If not: check equivalence/sufficiently similar			
10 Active ingredient manufacturing source	-		

Comparison of parameters for the local situation under review and a reference country			
Parameter	Describe/quantify the parameter for: Local situation (application)	Reference country (registration)	Remarks
11	Relevant metabolites (if identified)	-	
12	Co-formulants triggering a hazard classification	-	
13	Conclusion with respect to the pesticide product:		
	Use		
14	Crop or use situation		
15	Pest		
16	Dose rate (g product/ha), Number of applications per growing season, withholding period		
17	Conclusion with respect to the use:		
	Human health risks		
18	Use restrictions (human health)		
19	Required/recommended PPE		
20	Level of training/experience of operator		
21	Conclusion with respect to the human health risks: Risks similar or less when compared to the reference country		
	Environmental risks		
22	Use restrictions for bees		
23	Conclusion with respect to the environmental risks:		
24	Overall conclusions		

Annex 6 No Observed Adverse Effect Level (NOAEL)⁴²

For each human health toxicity study, if possible, the No Observed Adverse Effect Level (NOAEL) is derived. The NOAEL is the highest dose at which the most relevant critical effect (the adverse health effect that occurs first) is not yet observed (Figure 11). The Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose at which there was an observed toxic or adverse effect.

Sometimes the terms No Observed Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) may also be found in the literature. NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial effects of chemicals as well.

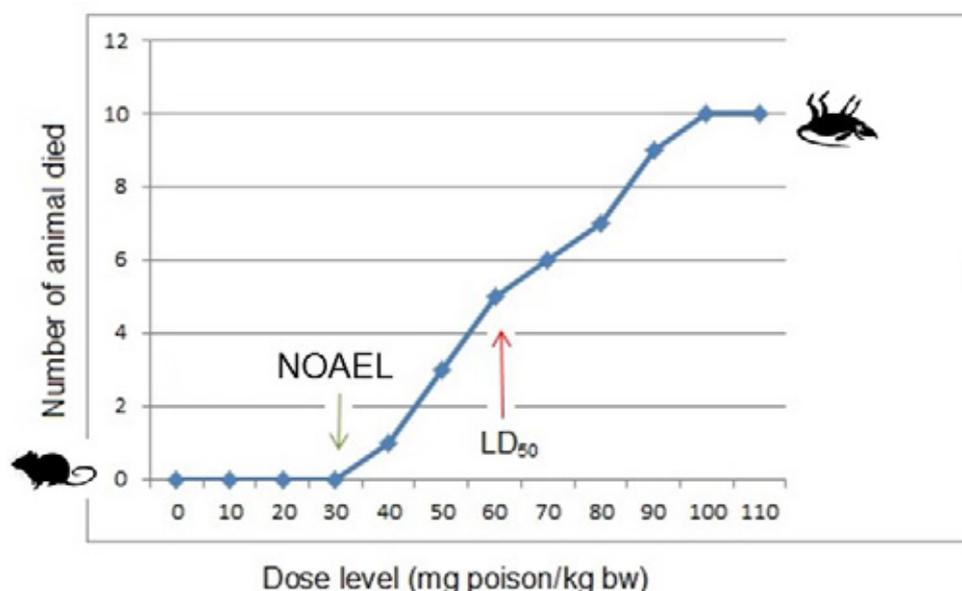


Figure 11 Illustrating the No Observed Adverse Effect Level (NOAEL) using an imaginary experiment with 10 animals.

For most end-points it is generally recognized that there is a dose or concentration below which adverse effects do not occur; for these, an NOAEL and/or LOAEL can be identified. For genotoxicity and carcinogenicity mediated by genotoxic mechanisms, dose-response is considered to be linear, meaning that risk cannot be excluded at any exposure level. A pesticide containing such an active ingredient can therefore not be authorized.

The lowest relevant NOAEL/LOAEL value should normally be used for risk characterization and the setting of acceptable exposure levels.

If the critical NOAEL/LOAEL is derived from an animal study, a default Uncertainty Factor (UF) of 10 is usually recommended to account for interspecies differences (WHO, 1994; WHO, 1999). In addition a default UF of 10 is used to account for inter-individual differences in the general population (WHO, 1994; WHO, 1999). Contributors to the overall UF are normally multiplied because they are considered to be independent factors; the most commonly used default UF for the setting of reference values for the general population is therefore $10 \times 10 = 100$ (WHO, 1994; WHO, 1999).

⁴² The content of this annex is taken from Annex 11 in Ter Horst et al. (2018).

In some cases, the use of additional UFs is justified. Situations in which additional UFs should be considered include the following:

- When LOAEL is used instead of NOAEL, an additional UF (e.g. 3 or 10) is usually incorporated,
- When an NOAEL from a sub-chronic study (in the absence of chronic study) is used to derive a reference value for long-term exposure, an additional UF (often 10) is usually incorporated to take account of the attendant uncertainties,
- If the critical NOAEL relates to serious, irreversible toxicity, such as developmental abnormalities or cancer induced by a non-genotoxic mechanism (WHO, 1999),
- When there are exposed subgroups, which may be extra-sensitive to the effects of the compound (e.g. neonates because of the incompletely developed metabolism),
- If the database is limited.

Annex 7 Instruction for downloading the EFSA AOEM model

EFSA AOEM is a tool assisting in the assessment of exposure of operators, workers, residents and bystanders to pesticides. This tool is proposed for pesticide registration purposes in Kenya to be used as part of the decision support scheme for human health risk assessments (Figure 6).

EFSA AOEM is part of a guidance document that sets out a (EU) harmonised methodology for calculating exposure to pesticides for four major population groups - operators, workers, residents and bystanders (EFSA, 2014). The user-friendly software tool consists of data spread sheets to quantify potential non-dietary, systemic exposure to pesticides. The tool can be downloaded as follows:

1. Go to the website for downloading the EFSA guidance (EFSA, 2014)
2. Scroll down and click on the section `Supporting information`
3. A drop down menu (Figure 12) appears from which a zip file containing the model can be downloaded.

The EFSA AOEM model is not suitable for some types of applications, such as dusting of crops before storage, seed treatment, spraying via airplane, fumigation of greenhouses.

The screenshot shows the EFSA Journal website page for the article 'Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products'. The page includes the EFSA logo, the journal title, and a 'Supporting Information' section. A table lists the files available for download, with a red arrow pointing to the file '3874Ax1-sup-0001.zip'.

Filename	Description
3874Ax1-sup-0001.zip Zip archive, 127K	Supplementary Material Files

Figure 12 Screen dump showing where to download the EFSA calculator assisting the assessment of exposure of operators, workers, residents and bystanders to pesticides.

Annex 8 Step by Step guidance for performing risk assessment for operators in the field

Short manual for using EFSA AOEM for exposure assessment of operators in the field

Once the zip file containing EFSA AOEM is downloaded (instructions are given in Annex 7) the spreadsheet can be extracted from the zip file.

It is advised to save the spreadsheet and name it so that the specific calculations for a product can be retrieved. For instance, a folder can be made for the specific product application and date of evaluation/application number. Within this folder, the calculation sheets used for the evaluation (non-dietary, dietary) can be saved. Each calculation spreadsheet should be labelled as well to indicate what was evaluated. For instance: 'EFSA AOEM 2015_NAME PRODUCT_USE EVALUATED.xlsm'.

In this case the name of the product is given, and the use that was evaluated (for instance upward manual spraying in citrus fruit).

The spreadsheet contains several data sheets with different functions: instructions, data entry, results, default values and fixed input for the different exposure assessments.

For the assessment of exposure of operators of outdoor spray applications the data sheet: 'Data entry' needs to be filled in and results of the assessment can be found in the data sheet: 'Operator Outdoor Spray AOEM'. Note that in the data sheet: 'Operator Outdoor Spray AOEM' some input from the user is needed as well. For the assessment of granular applications results of the assessment can be found in the data sheet: 'Operator Granules'.

The information required for the exposure assessment needs to be entered in the worksheet 'Data entry'. Note that the data entered here serves as input for all exposure assessments (operator, worker, residents and bystanders) in the spreadsheet.

The data entries of the 'Data entry' sheet (Figure 13) are discussed below in sequential order (from top to bottom of the sheet).

- The user may specify the substance name and the product name.
- The user needs to specify the RVNAS (Reference Value Non acutely toxic Active Substance); this term corresponds to the AOEL.
- The user may also specify the RVAAS (Reference Value Acutely toxic Active Substance). This term corresponds to the AAOEL (Acute Acceptable Operator Exposure Level) and is necessary for an acute risk assessment. However, at present for Kenya it is proposed to only perform a semi-chronic risk assessment for operators and workers. Therefore the RVAAS does not need to be specified.
- The user needs to select a crop type from the picklist. It is highly recommended that the PCPB drafts a list which specifies for each single crop to which crop group it belongs (e.g. the single crop broccoli belongs to the crop group brassica). This is necessary to prevent that user-subjectivity introduces variability into the results of the exposure assessment (i.e. different evaluators get different results due to the selection of a different crop group for the same crop).
- Considering the formulation type the user needs to select one of the four specified formulation groups. The formulation type is specified in the Table of Intended Uses/GAP table.
- The user needs to enter the minimum volume of water for application in L/ha (i.e. the minimum quantity of water, with which the pesticide product is to be applied). This corresponds to the entry 'Application rate – Water L/ha' specified in the Table of Intended Uses/GAP table.
- The user needs to enter the maximum application rate of the active substance in kg a.s./ha. This corresponds to the entry 'Application rate – g or kg a.i./ha' specified in the Table of Intended Uses/GAP table.

- The half-life for dissipation of the active substance on foliage needs to be specified. For Kenya it is proposed to use the default value of 30 days for organic chemicals, for which there is evidence of breakdown e.g. by photolysis or hydrolysis in soil or water.
- The amount of residue on foliage just after application (assuming no dissipation and assuming that everything is dislodgeable) should be specified. It might be considered to use the conservative value of 3 µg active substance/cm² of foliage/kg a.s. applied/ha.
- In case dermal absorption is not provided by the applicant, Kenya might adopt the EU approach (EFSA, 2017).

Table 2: Default values to be used in the absence of experimental data

Formulation category	Concentration status	Default value
Organic solvent-based ^(a) or other ^(b)	Concentrate	25%
	Dilution	70%
Water-based/dispersed ^(c) or solid ^(d)	Concentrate	10%
	Dilution	50%

(a): Formulation types: emulsifiable concentrate (EC), emulsion, oil in water (EW), suspo-emulsion (SE), dispersible concentrate (DC), oil miscible liquids (OL/OF), oil-based suspension concentrates (OD), emulsion for seed treatment (ES), microemulsion (ME).

(b): Formulation types: bait concentrate (CB), capsule suspension (CS), gel for direct application (GEL/GD), bait, ready for use (RB), mixture of capsule suspension and suspension concentrate (ZC), seed coated with a pesticide (PS), experimental solution of active substances in solvent (AI).

(c): Formulation types: soluble concentrate (SL), suspension concentrate (SC), flowable concentrate for seed treatment (FS), flowable (FL) (=SC).

(d): Formulation types: wettable powder (WP), water-dispersible granules (WG/WDG), water-soluble granules (SG), water-soluble powder (SP), powder for dry seed treatment (DS).

- In general, the percentage dermal absorption from a less concentrated product is in many cases higher than from a concentrated product (the more diluted the formulation, the higher the dermal absorption percentage). In case dermal absorption of in-use dilution is not provided by the applicant, the default values as shown in the table above can be applied.
- For oral absorption, the value derived from the ADME studies is used. In case this information is not provided by the applicant, for oral absorption a default value of 100% could be considered
- If information is not provided by the applicant, for inhalation absorption a default value of 100% could be considered
- The vapour pressure of the active ingredient is a data requirement in Kenya. The user should select from the picklist if the vapour pressure is below 5·10⁻³ Pa or between 5·10⁻³ Pa and 1·10⁻² Pa. For active substances with vapour pressures ≥ 10⁻² Pa, an ad hoc approach may be required. It is advised to address the latter in the follow up project.
- Outdoor application should be selected
- The user should select the application method from the picklist. At the moment manual application methods are very common for small holders in Kenya. Two types of manual application methods are available: 1) manual hand held and 2) knapsack. Please note that beforehand it might not be clear which one of these two is the worst case application method in the model, as the outcome depends on the application rate and possible protective equipment selected. It is up to the regulator to decide which of the application method is most appropriate.
- Buffer strips are not common practice in Kenya. Therefore the lowest values possible (2-3m for downward spraying; 5m for upward spraying) should be selected from the picklist.
- The user needs to enter the number of applications. This is specified in the Table of Intended Uses/GAP table.
- The user needs to enter the interval between multiple applications. This is specified in the Table of Intended Uses/GAP table.
- Specifying the season is not relevant for downward directed spraying applications, thus 'not relevant' should be selected from the picklist in case downward directed spraying is selected as application method.

	A	B	C	D	E	F
1	Note: Some drop-down menus depend on others. To avoid errors, please fill-in from top to bottom					
2						
3						
4	Substance name		<input type="text"/>			
5	Product name		<input type="text"/>			
6						
7	Reference value non acutely toxic active substance (RVNAS)		<input type="text"/>		mg/kg bw/day	
8	Reference value acutely toxic active substance (RVAAS)		<input type="text"/>		mg/kg bw/day	
9						
10	Crop type		<input type="text"/>			
11						
12	Substance properties					
13	Formulation type		<input type="text"/>			
14	Minimum volume water for application (liquids)		<input type="text"/>		L/ha	
15	Maximum application rate of active substance		<input type="text"/>		kg a.s. /ha	
16	50% Dissipation Time DT50		<input type="text"/>		30 days	
17	Initial Dislodgeable Foliar Residue		<input type="text"/>		3 µg/cm ² of foliage/kg a.s. applied/ha	
18	Dermal absorption of product		<input type="text"/>		100.00%	
19	Dermal absorption of in-use dilution		<input type="text"/>		100.00%	
20	Oral absorption of active substance		<input type="text"/>		100.00%	
21	Inhalation absorption of active substance		<input type="text"/>		100.00%	
22	Vapour pressure of active substance		low volatile substances having a vapour pressure of			
23			<input type="text" value="<5*10-3Pa"/>			
24	Scenario					
25	Indoor or Outdoor application		<input type="text" value="Outdoor"/>			
26	Application method		<input type="text" value="Downward spraying"/>			
27	Application equipment		<input type="text" value="Manual-Knapsack"/>			
28	Buffer strip		<input type="text" value="2-3"/>			
29	Number of applications		<input type="text"/>			
30	Interval between multiple applications		<input type="text"/>			
31	Season (upward spraying orchards only)		<input type="text" value="not relevant"/>			
32						
33						
34						
35						
36						
37						
38						

Instructions | **Data entry** | Summary | Operator Outdoor Spray AOEM | Operator Granules | Worker exposure | Resident exposure | Bystander

Figure 13 Screen dump of the Data entry sheet of the EFSA spreadsheet based calculator, part of its Guidance document on the assessment of exposure of operators and workers to pesticides.

The results of the semi-chronic risk assessment for operators is found on the sheet 'Operator Outdoor Spray AOEM' (Figure 14).

Operator exposure for test outdoor spray applications						
1	Operator exposure for test outdoor spray applications					
2	Application rate of active substance	0.5 kg a.s./ha	L AppRate			
3	Assumed area treated	4 ha/day	L AreaTreated			
4	Amount of active substance applied	2 kg a.s./day	L AmountAS			
5	Dermal absorption of the product	100.00%	L AbsorpProduct			
6	Dermal absorption of in-use dilution	100.00%	L AbsorpInuse			
7	Formulation type	Soluble concentrates, emulsifiable concentrate, etc.				
8	Indoor or Outdoor application	Outdoor				
9	Application method	Downward spraying				
10	Application equipment	Manual-Hand held				
11	Season	not relevant				
12						
13	Mixing and loading	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
14			75 th centile	95 th centile		
15		Hands	8281	30530	AOEM	
16		Body	5807	88092	AOEM	
17		Head	104	569	AOEM	
18		Protected hands (gloves)	54	396	AOEM	
19		Protected body (workwear or protective garment and sturdy footwear)	44	293	AOEM	
20		Protected head (hood and face shield)	2	32	AOEM	
21		Inhalation	5	28	AOEM	
22		Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
23	Gloves	No				
24	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model		
25	Head and respiratory PPE	None		1	1	
26	Water soluble bag	No		1		
27	User input					
28	Application	Exposure values	µg exposure/day applied		Reference	Comment
29			75 th centile	95 th centile		
30		Hands	2059	5617	AOEM	
31		Body	118491	182676	AOEM	
32		Head	16	113	AOEM	
33		Protected hands (gloves)	7	29	AOEM	
34		Protected body (workwear or protective garment and sturdy footwear)	11871	83507	AOEM	
35		Inhalation	35	35	AOEM	
36		Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
37		Gloves	No			
38	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model		
39	Head and respiratory PPE	None		1	1	
40	Closed cab	No		vehicle mounted upward spraying only		
41	User input					
42						
43	1. Total					
44		Without RPE/PPE	With RPE/PPE			
45	Longer term					
46	Total systemic exposure from mixing, loading and application (mg a.s./day)	134.7964303	22.4136172			
47	Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	2.2466072	0.3735603			
48	% of RVNAS	224.66%	37.36%			
49	<div style="border: 1px solid red; padding: 5px; display: inline-block;"> % of RVNAS (without or with PPE) should be used as exposure value in the final risk assessment for </div>					
50	Total systemic exposure from mixing, loading and application (mg a.s./day)	307.6616165	120.6930367			
51	Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	5.1276936	2.0115506			
52	% of RVAAS	#DIV/0!	#DIV/0!			
53						
54						

Figure 14 Screen dump of the Operator Outdoor Spray AOEM sheet of the EFSA spreadsheet based calculator, part of its Guidance document on the assessment of exposure of operators and workers to pesticides.

Results of exposure from mixing, loading and application are given for i) situations without any use of protective equipment (*without RPE/PPE*) and ii) situations with use of protective equipment (*with RPE/PPE*). For the latter, the user needs to select for both activities of the operator: 1) mixing and loading and 2) application the options for protective equipment:

- Gloves: Yes/No;
- Clothing: potential exposure/work wear – arms, body and legs covered;
- Head and respiratory PPE: none or 4 different PPE options

-
- Water soluble bag (mixing and loading only): Yes/No
 - Closed cab (application only + only relevant for tractor mounted spraying): Yes/No

For the final risk assessment for operators the total exposure (with or without PPE) as % of RVNAS (which corresponds to the total exposure as % of the AOEL) should be compared to AOEL from the hazard assessment.

Annex 9 Step by Step guidance for performing risk assessment for workers in the field

Short manual for using EFSA AOEM for exposure assessment of workers in the field

Worker exposure is defined as the exposure of a person who enters an area or handles crop previously treated with a plant protection product.

As explained in Annex 8, EFSA AOEM for exposure assessment of operators, workers, residents and bystanders contains several data sheets with different functions: instructions, data entry, results, default values and fixed input for the different exposure assessments. Note that the data entered here serves as input for all exposure assessments (operator, worker, residents and bystanders) in the spreadsheet.

For the assessment of exposure of workers in Kenya the data sheet: 'Data entry' needs to be filled in. The results of the assessment are found in the datasheet: 'Worker exposure'.

The data entries of the 'Data entry' sheet (Figure 13) are discussed in Annex 8

The results of the semi-chronic risk assessment for workers is found on the sheet 'Worker exposure' (Figure 15).

A 'Transfer Coefficient' (TC) is a theoretical estimate of the amount of contact (i.e. area of foliage) that occurs with a pesticide-treated crop during the conduct of a specific work activity. Dermal transfer coefficients are fixed and filled in automatically. The values for the dermal transfer coefficients are crop specific and can be found in the datasheet: 'Small tables' or more information can be found in the accompanying guidance document (EFSA 2014). Note that for the most protective option (hands, arms, body and legs covered) for several crops no values for transfer coefficients are available. Inhalation exposure may be due to vapour and/or airborne aerosols (including dust). For outdoor activities the inhalation potential is generally low and the inhalation route might only be of importance in exceptional cases. Therefore, the values for transfer coefficients are not given (i.e. default Not Applicable; NA – see sheet 'Default values') in the EFSA model.

For the final risk assessment for workers the total exposure (with or without PPE) as % of RVNAS (which corresponds to the total exposure as % of the AOEL) should be compared with AOEL from the hazard assessment.

1	Worker exposure from residues on foliage for test			
2	Crop type	Cereals		
3	Indoor or outdoor	Outdoor		
4	Application method	Downward spraying		
5	Application equipment	Manual-Hand held		
6	Worker's task	Inspection, irrigation		
7	Main body parts in contact with foliage	Hand and body		
8	Application rate of active substance	0.5 kg a.s./ha		L_AppRate
9	Number of applications	2		L_AppNb
10	Interval between multiple applications	14 days		L_AppInt
11	Half-life of active substance	30 days		d_HalfLifeAS
12	Multiple application factor	1.7		d_MAF
13	Dermal absorption of the product	100.00%		L_AbsorpProduct
14	Dermal absorption of the in-use dilution	100.00%		L_AbsorpInuse
15	Dislodgeable foliar residue (I_AppRate*I_DFR)	1.5 µg a.s./cm ²		d_DFR
16	Working hours	2 hr		d_WorkHr
17	Dermal transfer coefficient - Total potential exposure	12500 cm ² /hr		d_DermToUCV
18	Dermal transfer coefficient - arms, body and legs covered	1400 cm ² /hr		d_DermToCV1
19	Dermal transfer coefficient - hands, arms, body and legs cov	no TC available for this assessment		d_DermToCV2
20	Inhalation transfer coefficient for automated applications	NA ha/hr*10 ⁽⁻³⁾		d_InhalToAut
21	Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ⁽⁻³⁾		d_InhalToCut
22	Inhalation transfer coefficient for sorting / bundling	NA ha/hr*10 ⁽⁻³⁾		d_InhalToSort
23				
24	1. Total			
25		Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
26	Total systemic exposure (mg a.s./day)	64.6362982	7.2392654	no TC available for this assessment
27	Total systemic exposure per kg body weight (mg/kg bw/day)	1.0772716	0.1206544	
28	% of RVNAS	107.73%	12.07%	
29	<div style="border: 1px solid red; padding: 5px; display: inline-block;"> % of RVNAS (without or with PPE) should be used as exposure value in the final risk assessment for workers </div>			
30				
31		Systemic exposure		
32		[mg a.s. /day]	[mg a.s./kg bw/day]	
33	Dermal - Potential	64.6362982	1.0772716	F/1000*I_AbsorpInuse
34	Dermal - Work wear - arms, body and legs covered	7.2392654	0.1206544	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*I_AbsorpInuse
35	Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*I_AbsorpInuse
36	Inhalation			Na for outdoor activities
37				
38				
39				

Figure 15 Screen dump of the Worker exposure sheet of the EFSA spreadsheet based calculator, part of its Guidance document on the assessment of exposure of operators and workers to pesticides.

Annex 10 Step by Step guidance for performing risk assessment for residents

Short manual for using EFSA AOEM for exposure assessment residents

A resident is a person who lives, works, or attends school/institution adjacent to an area treated with a pesticide. The presence of a resident is incidental and unrelated to the work with the pest control products. The resident does not take action to avoid or control exposure. The exposure of a resident is long-term.

As explained in Annex 8, EFSA AOEM for exposure assessment of operators, workers, residents and bystanders contains several data sheets with different functions: instructions, data entry, results, default values and fixed input for the different exposure assessments. Note that the data entered here serves as input for all exposure assessments (operator, worker, residents and bystanders) in the spreadsheet.

For the assessment of exposure of residents in Kenya the data sheet: 'Data entry' needs to be filled in. The results of the assessment are found in the datasheet: 'Resident exposure'.

The data entries of the 'Data entry' sheet (Figure 13) are discussed in Annex 8

For the final risk assessment for residents the total exposure as % of RVNAS (which corresponds to the total exposure as % of the AOEL) should be compared with AOEL from the hazard assessment.

1	Resident exposure for BUGKIL					
2	Croptype	Fruiting vegetables				
3	Application method	Downward spraying				
4	Application equipment	Manual-Hand held			L_AppEquip	
5	Formulation type	Wettable powder, soluble powder			L_FormVal	
6	Buffer strip	2-3 m			L_Buffer	
7	Application rate of the product	0.09 kg a.s./ha			L_AppRate	
8	Concentration of active substance (in-use dilution for liquid applications)	0.15 g a.s./l			d_ConcAS	
9	Dermal absorption of product	100.00%			L_AbsorpProduct	
10	Dermal absorption of in-use dilution	100.00%			L_AbsorpInuse	
11	Oral absorption	100.00%			L_AbsorpOralinuse	
12	Dislodgeable foliar residue (i_AppRate*i_DFR)	0.27 µg a.s./cm ²			d_DFR	
13	Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa			L_Volat	
14	Concentration in air	0.001 mg/m ³			d_AirCon	
15	Resident dermal spray drift exposure 75th percentile - adult	0.47 ml spray dilution/person				
16	Resident dermal spray drift exposure 75th percentile - child	0.327 ml spray dilution/person				
17	Resident inhal. spray drift exposure 75th percentile - adult	0.00010 ml spray dilution/person				
18	Resident inhal. spray drift exposure 75th percentile - child	0.00022 ml spray dilution/person				
19	Resident dermal spray drift exposure mean - adult	0.22318 ml spray dilution/person				
20	Resident dermal spray drift exposure mean - child	0.18 ml spray dilution/person				
21	Resident inhal. spray drift exposure mean - adult	0.00009 ml spray dilution/person				
22	Resident inhal. spray drift exposure mean - child	0.00017 ml spray dilution/person				
23	Exposure duration dermal	2 hours			d_ReExpDur	
24	Exposure duration inhalation	24 hours			d_ReExpDurInhal	
25	Exposure duration entry into treated crops	0.25 hours			d_ExpDurTreatCrop	
26	Light clothing adjustment factor	18.0%			d_ClothAF	
27	Breathing rate adult	0.23 m ³ /day/kg			d_BreathRAAd	
28	Breathing rate child (1-3 year old)	1.07 m ³ /day/kg			d_BreathRCh	
29	Drift percentage on surface (75th percentile)	5.60%				
30	Drift percentage on surface (mean)	4.10%				
31	Turf transferable residues percentage	5.00%			d_Turf	
32	Transfer coeff. of surface deposits-adult	7300 cm ² /hour			d_ReTCAAd	
33	Transfer coeff. of surface deposits-child (1-3 year old)	2600 cm ² /hour			d_ReTCCCh	
34	Saliva extraction percentage	50.00%			d_SalExt	
35	Surface area of hands mouthed	20 cm ²			d_AreaHM	
36	Frequency of hand to mouth activity	9.5 events/hour			d_ReFreqHM	
37	Ingestion rate for mouthing of grass per day	25 cm ²			d_MouthGrass	
38	Dislodgeable residues percentage transferability for object to mouth	20.00%			d_DRP	
39	Transfer coefficient for entry into treated crops (75th percentile) - ad	7500 cm ² /h			d_TcEntryAd	
40	Transfer coefficient for entry into treated crops (75th percentile) - ch	2250 cm ² /h			d_TcEntryCh	
41	Transfer coefficient for entry into treated crops (mean) - adult	5980 cm ² /h			d_TcEntryAd	
42	Transfer coefficient for entry into treated crops (mean) - child	1794 cm ² /h			d_TcEntryCh	
43						
44	1. Total					
45	1.1 1-3 year old child					
46		Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
47	Total systemic exposure (mg a.s./day)	0.0402540	0.0107000	0.0207522	0.2278125	0.2297016
48	Total systemic exposure per kg body weight (mg/kg bw/day)	0.0040254	0.0010700	0.0020752	0.0227813	0.0229702
49	% of RVNAS	5.75%	1.53%			
50	1.2 Adult					
51		Spray drift	Vapour			
52	Total systemic exposure (mg a.s./day)	0.0578250	0.0138000			
53	Total systemic exposure per kg body weight (mg/kg bw/day)	0.0009638	0.0002300	0.0009198	0.0126563	0.0114524
54	% of RVNAS	1.38%	0.33%			

1-3 year old child: % of RVNAS should be used as exposure value in the final risk assessment for residents

Adult: % of RVNAS should be used as exposure value in the final risk assessment for residents

Figure 16 Screen dump of the Resident exposure sheet of the EFSA spreadsheet based calculator, part of its Guidance document on the assessment of exposure of operators and workers to pesticides.

Annex 11 Step by Step guidance for performing chronic risk assessment for consumers

Chronic risk assessment for consumers using the IEDI spreadsheet

The Microsoft Excel spreadsheet 'IEDI_calculation_vs04_17clusters.xlsm' is used for the chronic risk assessment for consumers.

The spreadsheet can be downloaded from the WHO GEMS website (WHO, 2019). Note, that updates of the spreadsheet are posted (with a different name than the one given above) and that the assessor should ensure that the latest version is used.

For the first tier it is good practice to adapt the spreadsheet according to specifications given on the sheet 'Manual' for situations where only MRLs are available:

If you have only MRLs, change the column titles (in GEMS_Food_diet and Final_table) into MRL and change "International Estimated Daily Intake" into International Theoretical Maximum Daily Intake (ITMDI) (in GEMS_Food_diet). Further proceed as for STMR.

After adapting the spreadsheet, it is good practice to rename the spreadsheet to for instance: 'IEDI_calculation_vs04_17clusters_first-tier.xlsm'

The spreadsheet contains four worksheet tabs with background information and default values: 'Clusters', 'GEMSfood data conversions', 'Rounded values' and 'Manual'. These tabs can be inspected. However, take care that you do not inadvertently change the values in the sheets (the tabs are not protected).

The tabs 'IEDI calculation' and 'Final_table' respectively are used to provide data and also display results.

Worksheet tab 'IEDI calculation'

In the worksheet tab 'IEDI calculation' the user needs to provide the compound name, the compound number, the ADI (in yellow cells) and depending on the tier the MRLs or STMRs or STMR-Ps for relevant commodities (in yellow columns). In case of using MRLs an ITMDI is calculated instead of an IEDI.

It is the responsibility of the assessor to link the crop in the table of intended uses (or GAP table) to relevant commodities in the sheet 'IEDI calculation'.

The spreadsheet contains the food category system of the Codex Alimentarius (Codex, 2017).

This food category system is hierarchical and classifies foods into groups and/or sub-groups.

Commodities are classified into groups, subgroups and single commodities/foods

So you have:

1. Group
 - 1.1. Subgroup
 - 1.1.1. Commodities

For instance Group 006 'assorted tropical and subtropical fruits-inedible peel' was divided into six subgroups which included the subgroup 006B smooth peel-large. Subgroup 006B smooth peel-large contains different agricultural crops each with an unique code (for instance the fruit mango with code FI 0345). Different commodities of mango are listed i.e. Mango, raw (incl. canned mango, incl. mango juice), Mango, raw (incl. canned mango, excl. mango juice), Mango, raw (incl. mango juice, excl. canned mango), Mango, juice, Mango, canned. It is up to the assessor to judge which of these different commodities are relevant for his/her country.

If a MRL, STMR or STMR-P is assigned to a 'Group' one should NOT assign a MRL, STMR or STMR-P to a subgroup or a single commodity that belongs to the group. If done however the consequence will be that consumption of the subgroup/single commodity will be accounted for twice. The same holds for assigning a MRL, STMR or STMR-P to a subgroup and at the same time also assigning a MRL, STMR or STMR-P to a single commodity which belongs to the subgroup.

A suggestion for future use of the IEDI spreadsheet in Kenya is to differentiate between commodities relevant and not relevant for Kenya by marking the commodities irrelevant for Kenya in red.

Once the assessor provides the compound name, the compound number, the ADI and the MRL, STMR or STMR-P for relevant commodities, the 'make IEDI table' needs to be clicked.

Results of the assessment can be viewed in the worksheet tab 'Final_table'.

Summarizing, the steps are as follows:

1. Select tab 'IEDI calculation'
2. Provide compound name, compound number and ADI (in yellow cells)
3. Provide the MRL, STMR or STMR-P for relevant commodities (in yellow columns)
4. Start calculations by clicking on the button 'Make IEDI table'
5. Select tab 'Final_table' to examine the result of the assessment

Read the information on the worksheet tab 'Manual' carefully as it contains more detailed information than this annex.

Worksheet tab 'Final_table'

As long as Kenya has not established a national food consumption pattern, it is proposed to use the dietary data of the WHO GEMS43 Cluster Diet 13 (WHO, 2012) as a best approximation.

In the tab Final_table the results of the G13 diet needs to be examined. The number in the cell indicating the total dietary exposure (ITMDI) as percentage of ADI is the final result of the chronic risk assessment for consumers (Figure 17).

If this percentage is above 100%, then adverse effects on consumers cannot be excluded (unacceptable risks) and authorisation should not be granted.

In the IEDI spreadsheet, the dietary intake of any particular pesticide residue is obtained by multiplying the residue level in the food by the amount of commodity consumed from the WHO GEMS⁴⁴ Cluster Diet 13. Total intake of the pesticide residue is consequently obtained by summing the intakes from all commodities containing the residue concerned.

⁴³ Global Environment Monitoring System (for monitoring and assessment of food contamination).

⁴⁴ Global Environment Monitoring System (for monitoring and assessment of food contamination).

a.i. (j)		International Estimated Daily Intake (IEDI)										ADI = 0 - 0.04 mg/kg bw		
Codex Code	Commodity description	Expr as	STMRL mg/kg	Dietary intake (ug/person/day)			Residues (ug/kg)			ADI (ug/person/day)				
				G13 diet	G13 intake	G1 intake	G16	G17	G17	intake	diet	intake		
FC 0001	Group of Citrus fruit, raw (incl citrus fruit juice, incl kumquat commodities)	RAC	0.9	21.16	19.04	2.9	0.68	0.76	0.08	0.01	0.00	20.12	2.01	
FI 0345	Mango, raw (incl canned mango, incl mango juice)	RAC	0.1	12.25	1.23	6.83	0.68	0.76	0.08	0.01	0.00	26.42	2.64	
FI 0350	Papaya, raw	RAC	0.1	6.47	0.65	0.25	0.03	0.19	0.02	0.01	0.00	24.94	2.49	
FI 0353	Pineapple, raw (incl canned pineapple, incl pineapple juice, incl dried pineapple)	RAC	0.1	8.51	0.85	6.27	0.63	6.89	0.69	0.18	0.02	0.04	0.01	
VC 0424	Cucumber, raw	RAC	0.3	0.68	0.20	1.81	0.54	10.40	3.12	0.01	0.00	0.04	0.01	
VC 0432	Watermelon, raw	RAC	0.2	4.29	0.86	0.30	0.06	28.70	5.74	0.01	0.00	NC	-	
VO 2045	Subgroup of tomatoes, raw (incl processed) (Lycopersicum spp. Only)	RAC	0.5	15.50	7.75	5.78	2.89	71.52	35.76	2.00	1.00	12.50	6.25	
VO 0051	Subgroup of peppers, raw (incl dried sweet peppers, excl dried chilipeppers), incl okra	RAC	0.7	15.20	10.64	14.23	9.96	25.14	17.60	0.91	0.64	NC	-	
VP 0061	Beans with pods (Phaseolus spp): (immature pods + succulent seeds)	RAC	0.15	NC	-	NC	-	NC	-	NC	-	NC	-	
VP 0062	Beans without pods: (Phaseolus spp.) (succulent seeds), raw	RAC	0.15	0.30	0.05	3.13	0.47	4.11	0.62	0.01	0.00	NC	-	
VP 2063	Subgroup of succulent peas without pods	RAC	0.15	0.21	0.03	0.02	0.00	5.51	0.83	0.02	0.00	NC	-	
VD 0071	Beans, dry, raw (Phaseolus spp)	RAC	0.15	7.11	1.07	2.33	0.35	3.76	0.56	44.70	6.71	3.27	0.49	
VD 0527	Cowpea, dry, raw (Vigna sinensis, Dolichos sinensis)	RAC	0.15	12.77	1.92	0.99	0.15	0.01	0.00	4.33	0.65	NC	-	
VR 0574	Beetroot, raw	RAC	-	-	-	-	-	-	-	-	7.91	0.79		
VR 0577	Carrots, raw	RAC	-	-	-	-	-	-	-	-	NC	-		
VR 0463	Cassava raw (incl starch, incl tapioca, incl flour) (i.e. Manioc)	RAC	-	-	-	-	-	-	-	-	45.48	11.37		
GC 0081	Cereal grains, excl pseudocereals, excl sweet corn (incl processed)	RAC	-	-	-	-	-	-	-	-	263.09	131.55		
GS 0659	Sugar cane, raw (incl sugar, incl molasses)	RAC	-	-	-	-	-	-	-	-	45.70	31.99		
-	-	-	-	-	-	-	-	-	-	-	-	-		
Total intake (ug/person)=				293.4	298.9	372.8	192.8	194.2						
Bodyweight per region (kg bw) =				60	60	60	60	60						
ADI (ug/person)=				2400	2400	2400	2400	2400						
%ADI=				12.2%	12.5%	15.5%	8.0%	8.1%						
Rounded %ADI=				10%	10%	20%	8%	8%						

For Kenya examine results of cluster diet G13

Final result of the chronic risk assessment for consumers. If the total dietary chronic exposure (ITMDI or IEDI) is < 100% of ADI, then no adverse effects on consumers are expected (acceptable risks).

Figure 17 Screen dump of the tab Final_table of the IEDI spreadsheet.

Issues regarding the use of the IEDI spreadsheet in Kenya:

- By using the MRL as input, the International Theoretical Maximum Daily Intake (ITMDI) will be calculated instead of the International Estimated Daily Intake (IEDI). The column titles need to be changed accordingly in the spreadsheet. By using the MRL as input the results of the risk assessment will be more worst case (from a regulatory point of view) than when using the mean residues from supervised trails.
- If registration is asked for product X containing active ingredient Y. GAP tables of all pest control products containing active ingredient Y should be retrieved from the dossiers. Using this information a list should be made of all crops which potentially can contain residues of active ingredient Y due to the registration of pesticide products containing active ingredient Y.

The risk assessment for consumers in Kenya will be done by comparing the exposure (result of the WHO IEDI spreadsheet; which is the total dietary exposure as percentage of the ADI) to the hazard (ADI).

Deciding whether risk are acceptable or not is done according:

- No adverse effects on humans expected (acceptable risks) if:
 - Total dietary exposure (ITMDI or IEDI) is ≤ 100% of ADI
- Adverse effects on humans cannot be excluded (unacceptable risks) if:
 - Total dietary exposure (ITMDI or IEDI) is >100% of ADI

Annex 12 Step by Step guidance for performing acute risk assessment for consumers

Acute risk assessment for consumers using the IEDI spreadsheet

The Microsoft Excel spreadsheet 'IESTI_calculation20_model.xlsm' is used for the acute risk assessment for consumers. IESTI is an abbreviation of: International estimated short-term intake.

The spreadsheet can be downloaded from the WHO GEMS website (WHO, 2019). Note, that updates of the spreadsheet are posted (with a different name than the one given above) and that the assessor should ensure that the latest version is used.

The spreadsheet contains two worksheet tabs with background information: 'Abbreviations' and 'Manual'. These tabs can be inspected.

The tabs 'IESTI calculation' and 'Final_table' respectively are used to provide data and also display results.

Worksheet tab 'IESTI calculation'

In the worksheet tab 'IEDI calculation' the user needs to provide the compound name, the compound number, the ARfD (in yellow cells) and the STMRs or STMR-Ps and HRs or HR-Ps for relevant commodities (in yellow columns) (Figure 18).

HR	highest residue in composite sample of edible portion found in supervised trials from which the MRL or STMR was derived, in mg/kg
HR-P	highest residue in the processed commodity, in mg/kg, calculated by multiplying the HR in the raw commodity by the processing factor bw body weight, in kg, provided by the country for which the large portion, LP, was used
STMR	supervised trials median residue, in mg/kg
STMR-P	supervised trials median residue in processed commodity, in mg/kg

It is the responsibility of the assessor to link the crop in the table of intended uses (or GAP table) to relevant commodities in the sheet 'IESTI calculation'.

The spreadsheet contains the food category system of the Codex Alimentarius (Codex, 2017). More information and some guidance are provided in Annex 11.

Once the assessor provides the compound name, the compound number, the ARfD and the STMRs or STMR-Ps and HRs or HR-Ps for relevant commodities, the button 'make finale table adults&children' needs to be clicked. Results of the assessment can be viewed in the worksheet tab 'Final_table'.

In order to view the results for women, go back the sheet 'IESTI calculation' and click the button 'make final table women'. Results of the assessment can be viewed in the worksheet tab 'Final_table'.

Read the information on the worksheet tab 'Manual' carefully as it contains more detailed information than this annex.

Can assess different exposure groups

The screenshot shows a spreadsheet with columns A through AP. Key features include:

- Two green callout boxes at the top: "Make final table adults&children" (pointing to column 13) and "Make final table women" (pointing to column 18).
- Yellow callouts: "yellow cells allowed to be changed", "Automated entry via entry in final row", and "First enter STMR and then IR".
- Text: "INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (ESTI)", "Version 16.4.4.28 August 2017", and "All data, all population groups".
- Table headers: Code, Commodity, Processing, wt, STMR or IR or IR-P, det con Preset factor codes (see 1, case 2), Country, Population group, n Exposed as, Large portion, g/person, Unit weight, g/kg, Toxicity factor, Case, % acute RfD rounded, Young children (0 months - 6 yrs), Country, Population group.
- Table rows: 9-25, including commodities like CITRUS FRUITS, Lemons and Limes, and various lemon and lime products with their respective processing methods and exposure parameters.
- A large red circle highlights a significant portion of the table data.
- A green circle at the bottom left highlights the text "IESTI calculation".

Data included from different countries (large portion, unit weight) for each commodity

Figure 18 Screen dump of the tab 'IESTI calculation' of the IESTI spreadsheet.

Worksheet tab 'Final_table'

Results of the assessment can be viewed in the worksheet tab 'Final_table'. The IESTI is given as percentage of ARfD for adults (general population), children and women (Figure 19).

Results general population and children

thiacloprid (0)														IESTI		
Acute RfD= 0,03 mg/kg bw (30 µg/kg bw)														Maximum %ARfD:		
														70%	40%	70%
														all	gen pop	child
Codex Code	Commodity	Processing	STMR or STMR-P mg/kg	HR or HR-P mg/kg	DCF	Country	Population group	n	Large portion, g/person	Unit weight, edible portion, g	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded	% acute RfD rounded	% acute RfD rounded
FP 0226	Apple (all commodities)	highest utilisation: raw with peel (incl consumption without peel)	0,3	0,3	1,000	CN	Child, 1-6 yrs	1314	403,39	255,0	3	2a	1,52 - 16,98	5% - 60%	2% - 30%	5% - 60%
VC 0046	Melons, except watermelon (all commodities)	highest utilisation: Total	0,2	0,2	1,000	PRIM O-BE	Child	P97,5	540,00	540,0	3	2b	0,01 - 18,2	0% - 60%	0% - 30%	0% - 60%
VC 0424	Cucumber (all commodities)	highest utilisation: raw with skin	0,5	0,5	1,000	CN	Child, 1-6 yrs	340	212,11	458,1	3	2b	0,19 - 19,72	1% - 70%	0% - 40%	1% - 70%

thiacloprid (0)														IESTI		
Acute RfD= 0,03 mg/kg bw (30 µg/kg bw)														Maximum %ARfD:		
														30%		
														women		
Codex Code	Commodity	Processing	STMR or STMR-P mg/kg	HR or HR-P mg/kg	DCF	Country	Population group	n	Large portion, g/person	Unit weight, edible portion, g	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded		
FP 0226	Apple (all commodities)	highest utilisation: canned babyfood	0,3	0,3	1,000	NL	gen pop, > 1 yrs	7	1363,51	NR	NR	3	0,6 - 6,22	2% - 20%		
VC 0046	Melons, except watermelon (all commodities)	highest utilisation: Total	0,2	0,2	1,000	CA	women, 15-49 yrs	179	1254,36	997,9	3	2a	0 - 9,65	0% - 30%		
VC 0424	Cucumber (all commodities)	highest utilisation: cooked/boiled (without skin)	0,5	0,5	1,000	NL	gen pop, > 1 yrs	E	200,03	333,0	3	2b	0,08 - 4,56	0% - 20%		

Results women

Final_table

Figure 19 Screen dump of the tab 'Final_table' of the IESTI spreadsheet.

Annex 13 Background information relevant for the consumer/ dietary risk assessment

Plant metabolism and residue definition

Crops

To assess the fate of residues of active substances, metabolism studies need to be performed in plants representative of crops in which use of the active is intended, under conditions corresponding to the intended GAP and, using a radiolabelled form of the active substance.

OECD guideline 501 (OECD, 2007a) describes how to correctly perform metabolism studies.

Metabolism studies do not need to be performed for every crop in which use of the active is intended. A distinction is made between five different crop groups:

- Leafy crop
- Root/tuber crop
- Fruit
- Cereal
- Pulses/oilseeds.

For the classification of crops, reference is made to OECD guideline 501 (OECD, 2007a). The method of application, e.g. foliar spray, soil or seed treatment, should be representative of the intended use. If the metabolism of the active substance is similar in three different plant groups investigated, metabolism is assumed similar in all crop groups and further study is not required.

A residue definition for plant products is derived from the data from plant metabolism studies, performed with an appropriate crop group and according to a GAP similar as applied for, using radiolabelled active substance(s) of the pest control product. Since the primary purpose of a metabolism study is to identify the chemical components of the residue, the maximum application rate (the proposed GAP application rate) should be used to allow for characterization and/or identification of the residue. Please note that when low levels of residue in crops are expected from the maximum application rate, experiments at exaggerated rates may be needed to aid metabolite identification.

The residue definition is established by taking the following principal points into account:

- The residue definition (for enforcement/ monitoring) must be suitable for routine monitoring, and should preferably be as reliable and as simple as possible in order not to hinder robust monitoring (*i.e.* the use of multi residue methods)
- The residue definition (for risk assessment) should include the toxicologically relevant metabolite(s) and/or the active substance and the components that constitute the largest part of the residue.

In principle all residues >0.05 mg/kg and/or >10% of total residue (TRR, total radioactive residue) will be included in the residue definition for risk assessment unless proven toxicologically irrelevant. The dose rate applied in the metabolism study should not be too low, as this could result in too small fractions to identify the metabolites. Applying too high dose rates can alter metabolic pathways due to saturation of enzymatic processes, and may therefore cause results which are not representative for the intended use.

Whether a metabolite needs to be included in the residue definition, depends on its toxicity. EFSA provides guidance on the establishment of the residue definition to be used for dietary risk assessment (EFSA, 2016).

Supervised residue trials

To determine the amount of residues expected after the use of a pesticide product, trials are performed that represent the commercial and agricultural use of the pesticide product. The trials should be performed in accordance with the proposed worst-case use on the label.

The worst-case use can be determined by taking the prescribed highest dose rate, maximum number of applications, the shortest spray interval and the shortest pre-harvest interval. The trials are not performed with radiolabelled material, but with a formulated product.

OECD guideline 506 (OECD, 2007b) describes how to correctly perform supervised residue trials.

The crop residue trials that serve for derivation of MRLs in plant products must be carried out in accordance with the requested directions for use, in accordance with the most critical use where several directions for use are concerned and under GLP. It is also required that the relevant residue components are analysed at the time of harvest, *i.e.* the residues in the residue definition for risk assessment. Where the products contain residues above the limit of quantification, consisting of an edible and a non-edible part, these must be analysed separately to be able to derive a processing factor, which can be used for refinement of the consumer risk assessment, e.g. citrus analysis in both peel and pulp, stone fruits in both stone and flesh.

A quick scan can be performed on the supervised residue trials by taking into account the following check points:

- Application rates, interval and PHI (pre-harvest interval, time between (last) application and harvest) in accordance with the critical use;
- Weather details – large amounts of precipitation on the day of application can negatively influence residue levels;
- Indoor/outdoor – is the use applied for indoor or outdoor and are the trials performed accordingly;
- Varieties used – using different varieties of a crop can result in different results;
- Sample size – is the sample size taken large enough to represent a reliable sample? This varies per crop. A very detailed list of sample sizes is presented in EU guideline 7029/VI/95 rev.5 of July 22nd, 1997, appendix B: General recommendations for the design, preparation and realization of residue trials (EU, 1997);
- Storage of samples – were the samples taken stored frozen shortly after sampling, during transport and at testing facility. Not freezing samples can result in underestimated levels due to degradation of residues after sampling;
- Analytical method used – is the method used acceptable for the pesticide concerned and are recovery rates acceptable in accordance with guidelines.

Were the requested use concerns a group of comparable products, determination of the residues in one or more representatives of the group is sometimes sufficient and results may then be extrapolated to related crops. The EU provides guidelines on comparability, extrapolation, group tolerances and data requirements for pesticides residues in food and raw agricultural commodities (EU, 2017).

Samples taken from metabolism studies and from supervised residue trials will deteriorate in quality and residues can decline when samples are not stored appropriately. OECD 506 is the guideline on 'Stability of Pesticide Residues in Stored Commodities' (OECD, 2007b).

Maximum Residue Levels

Definition and legislation

Maximum Residue Levels or Maximum Residue Limits (MRLs) are the legal limits (concentrations) for pesticide residues (mg/kg) in food commodities and animal feed. MRLs are established worldwide, with different legislation for countries/regions.

Europe, US and Japan for example all have their own legislation and consequently, their own limits.

There is also a global forum that established MRLs: Codex Alimentarius Commission. The Codex Alimentarius Commission was established by FAO and WHO in 1963. It develops harmonised international food standards, guidelines and codes of practice to protect the health of the consumers and ensure fair practices in the food trade.

One organisation (EU) and 189 countries, including Kenya, are members of Codex.

MRL sources

MRLs can either be obtained from databases or they can be calculated using results from supervised residue trials or analytical measurements.

The MRL can subsequently be used for a national risk assessment or to compare analysed residue levels with the MRLs set in the country to which crops are exported. A single analytical measurement cannot be used to establish an MRL since multiple results are needed to form a dataset, but it can be used to check whether a batch of a crop complies with the MRL in the importing country. The flow chart in Figure 20 shows how MRL setting for national risk assessment and export is done in many countries.

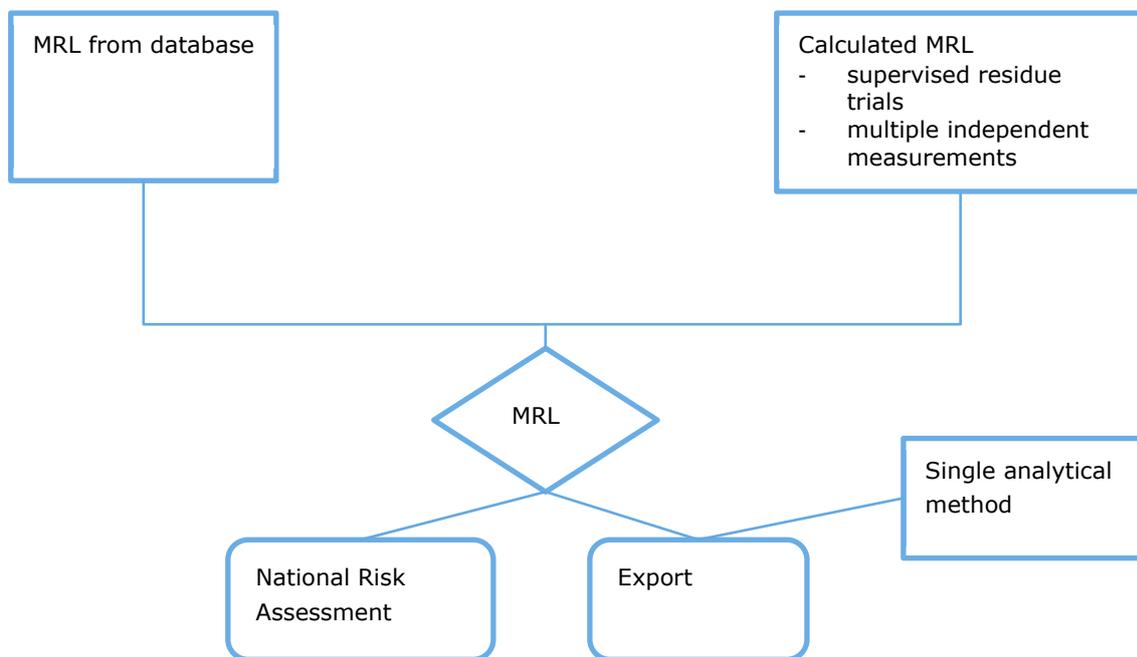


Figure 20 Flow chart for MRL setting for national risk assessment and export – as used by many countries.

The most relevant databases for MRLs are listed in the FAO pesticide registration toolkit (FAO, 2019) and repeated below. In case the links to the website in the text below are outdated, it is advised to use the links in the FAO pesticide registration toolkit. These links are regularly updated.

International sources

Codex Alimentarius

The main principal international source of MRLs is the Codex Alimentarius. MRLs are set by the Codex Committee on Pesticide Residues (CCPR), based on recommendations made by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR).

MRLs can be found in the Codex pesticides in food online database (Codex, 2019):

<http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/pesticides/en/> (website last

entered: 4 November 2019). The database can be searched by pesticide common name or class as well as by commodity name or code.

Global MRL database

The United States Department of Agriculture (USDA) used to maintain an international database of MRLs. This database is now managed by Bryant Christie Inc., as the Global MRL database: <https://www.globalmrl.com/> (website last entered: 4 November 2019). A (free) registration is required to access this database. The free subscription only provides access to the U.S. MRLs.

New Zealand MRL web page

The New Zealand Ministry of Primary Industries maintains a web page on pesticide maximum residue limit (MRL) legislation around the world: <http://www.foodsafety.govt.nz/industry/sectors/plant-products/pesticide-mrl/worldwide.htm> (website last entered: 4 November 2019). Links are provided to a large number of national authorities that set MRLs, as well as to their MRL databases if available.

National/regional sources of MRL data

European Union

The European Commission sets its MRLs applicable in the EU (referred to as maximum residue levels), which are not always the same as Codex MRLs: <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.selection&language=EN> (website last entered: 4 November 2019).

The EU MRL database can be searched by pesticide common name or by commodity or commodity groups. For the products and the part of the product to which EU-MRL's apply, see Annex 1 of Regulation (EU) No 396/2005 (most recent updated by Regulation (EU) No 752/2014) (<http://eur-lex.europa.eu/homepage.html>; website last entered: 4 November 2019).

United States of America

The US Environmental Protection Agency (US-EPA) sets pesticide residue tolerances applicable in the USA. The official publication of pesticide tolerances for the USA is in the e-Code of Federal Regulations (e-CFR). The US-EPA provides guidance on how to obtain MRLs for specific commodities through the e-CFR (<https://www.epa.gov/pesticide-tolerances/how-search-tolerances-pesticide-ingredients-code-federal-regulations>; website last entered: 4 November 2019).

US tolerances can also be accessed through the *Global MRL database*, mentioned under international sources.

Australia

Australian MRLs are published in the Agricultural and Veterinary Chemicals Code Instrument No. 4 (MRL Standard). The MRL Standard can be accessed through the Australian Pesticides and Veterinary Medicines Authority (<https://apvma.gov.au/node/10806> : click on the link to the ComLaw website; website last entered: 4 November 2019).

New Zealand

The MRLs applicable in New Zealand are published in the New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards (<https://www.mpi.govt.nz/processing/agricultural-compounds-and-vet-medicines/maximum-residue-levels-for-agricultural-compounds/>; website last entered: 4 November 2019). Click on the link 'Maximum residue levels (MRLs) for agricultural compounds - Food notice' on this website to obtain the most recent version of the standards.

Derivation of endpoints and reference values for consumer risk: MRL, STMR and HR for plant products

Three mathematical values can be derived from supervised residue trials which are needed for consumer risk assessment:

- STMR (Supervised Trial Median Residue) is the median residue value from the residue trials, which can be used for refined chronic and acute intake calculations and feeding studies;

-
- HR (Highest Residue) value is the highest value measured in a residue trial and can be used for acute intake calculations;
 - MRL (Maximal Residue Level) is the maximum concentration of residue, calculated by using a statistical formula and results from supervised residue trials, which can be used for chronic and acute diet calculations for man, as a first tier. Derivation of the MRL is described below.
- MRL calculation has been harmonised by the use of the OECD calculator, developed in 2011. As input parameters the results of the acceptable supervised residue trials at the prescribed pre-harvest intervals are used:

The spreadsheet and a guide can be found at:

<http://www.oecd.org/env/chemicalsafetyandbiosafety/agriculturalpesticidesandbiocides/oecdmaximumresiduelimitcalculator.htm> (website last entered: 4 November 2019).

Where no residues at all are found above the LOQ (Limit of Quantification), the STMR (Supervised Trial Mean Residue), HR (Highest Residue) and MRL are based on the LOQ. Where there are indications that residue levels are really zero (because the residue levels in the overdosed trials are also < LOQ) the STMR and HR are set at 0 and the MRL at the LOQ.

Wageningen Environmental Research
P.O. Box 47
6700 AA Wageningen
The Netherlands
T +31 (0)317 48 07 00
www.wur.nl/environmental-research

Wageningen Environmental Research
Report 2979
ISSN 1566-7197

The mission of Wageningen University & Research is "To explore the potential of nature to improve the quality of life". Under the banner Wageningen University & Research, Wageningen University and the specialised research institutes of the Wageningen Research Foundation have joined forces in contributing to finding solutions to important questions in the domain of healthy food and living environment. With its roughly 30 branches, 5,000 employees and 10,000 students, Wageningen University & Research is one of the leading organisations in its domain. The unique Wageningen approach lies in its integrated approach to issues and the collaboration between different disciplines.



To explore
the potential
of nature to
improve the
quality of life



Wageningen Environmental Research
P.O. Box 47
6700 AB Wageningen
The Netherlands
T +31 (0) 317 48 07 00
www.wur.eu/environmental-research

Report 2979
ISSN 1566-7197

The mission of Wageningen University & Research is "To explore the potential of nature to improve the quality of life". Under the banner Wageningen University & Research, Wageningen University and the specialised research institutes of the Wageningen Research Foundation have joined forces in contributing to finding solutions to important questions in the domain of healthy food and living environment. With its roughly 30 branches, 5,000 employees and 10,000 students, Wageningen University & Research is one of the leading organisations in its domain. The unique Wageningen approach lies in its integrated approach to issues and the collaboration between different disciplines.

